COMPARATIVE STUDY ON SAFETY AND EFFICACY OF IRON ISOMALTOSIDE VERSUS IRON SUCROSE IN PATIENTS OF ANEMIA IN CHRONIC KIDNEY DISEASE STAGE 3-5 ND

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DECLARATION BY THE CANDIDATE

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Dedicated

to

my family

&

Teachers

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Dr. Deepali Kaushal

ABBREVIATIONS

CKD	–Chronic Kidney Disease
ND	-Non dialysis Dependent
IIM	-Iron Isomaltoside
IS	–Iron Sucrose
IDA	–Iron Deficiency Anemia
Hb_	-Hemoglobin
TSAT	- Transferrin Saturation
eGFR	- Estimated Glomerular Filtration Rate
AE	- Adverse Effects
ESA	- Erythropoiesis Stimulating Agents
DM	- Diabetes Mellitus

ABSTRACT

Background: Anemia is a common complication in chronic kidney disease (CKD) patients, with a multifactorial pathophysiology involving impaired erythropoiesis, decreased erythropoietin production, and dysregulated iron metabolism. Intravenous iron supplementation is crucial in managing this condition, but the optimal formulation remains debated.

Aims and Objectives: This study aimed to compare the safety and efficacy of iron isomaltoside versus iron sucrose in patients with anemia in CKD stages 3-5 (not on dialysis).

Methods: A prospective comparative study was conducted with 100 CKD patients randomized into two groups of 50 each. Group 1 received a single 1000mg dose of iron isomaltoside, while Group 2 received iron sucrose in 200mg IV injections up to five times over two weeks. Hemoglobin, transferrin saturation (TSAT), and ferritin levels were measured at baseline, 2, 4, and 8 weeks. Adverse reactions were monitored throughout the 10-week study period.

Results: Iron isomaltoside demonstrated superior efficacy compared to iron sucrose. By the 8th week, 90% of patients in the iron isomaltoside group achieved a ≥1 g/dL increase in hemoglobin, compared to 50% in the iron sucrose group ($p=0.001$). The iron isomaltoside group also showed significantly greater improvements in TSAT (mean difference 8.13%, $p=0.001$) and ferritin levels (mean difference 77.23 ng/mL, $p=0.001$) at 8 weeks. A higher proportion of patients in the iron isomaltoside group reached target TSAT levels of 20-50% (94% vs 76%, $p=0.023$) and ferritin >100 ng/mL (98% vs 62%, $p=0.001$). Both treatments showed comparable safety profiles with no significant differences in adverse reactions.

Conclusion: Iron isomaltoside demonstrates superior efficacy to iron sucrose in treating anemia among CKD patients, with significant improvements in hemoglobin, TSAT, and ferritin levels. The single-dose regimen of iron isomaltoside offers a more convenient treatment option without compromising safety. These findings suggest iron isomaltoside as a preferred treatment for anemia in CKD patients, potentially improving patient compliance and reducing the frequency of hospital visits for iron administration.

Keywords: Iron Isomaltoside, Iron sucrose, Erythropoiesis Stimulating Agents, Diabetes Mellitus, Hemoglobin, Transferrin Saturation.

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INTRODUCTION

Chronic kidney disease (CKD) prevalence has increased in recent decades and has become a global public health challenge, requiring more costs.[1] Recently, CKD is found in more than 500 million people and constitutes 11% population. [2] Anemia is a known complication in chronic kidney disease (CKD) patients, with a multifactorial pathophysiology involving impaired erythropoiesis, decreased erythropoietin (EPO) production, and dysregulated iron metabolism. Anemia due to CRF occurs if GFR is approximately 60 mL/min/1.73m2, and the frequency increases if GFR drops below 30 mL/min/1.73m2.[3]

Traditionally, anemia is defined based on serum hemoglobin level; serum transferrin saturation (TSAT) and serum ferritin. The KDIGO guidelines define anemia as Hb < 13 g/dL in males and <12 g/dL in females.[4]

For instance, anemia is prevalent in 14% CKD population in USA, 39.36% in India, 51.5% in China, 43.18% in South Africa, and 79% in Cameroon. Moreover, the prevalence increases with the CKD stage, with an overall prevalence of 22.4%, 41.3%, and 53.9% in CKD stages 3, stage 4 and stage 5, respectively.[5]

CKD-AA is mainly due to EPO-H deficiency, but iron, folate and vitamin B12 deficiency also can cause anemia in CKD patients. However, secondary hyperparathyroidism and uremic bone marrow suppression, including other common associated chronic diseases, are also contributory causes of CKD-AA. IDA in CKD patients occurs either due to real (absolute or true) and/or functional iron deficiency. Actual IDA occurs because of severe reduction of stored iron in spleen, liver, and bone marrow. On the contrary, in functional iron deficiency, the iron body storage is either normal or increased, but the iron is not

available for RBC formation. The main reason for reduced iron availability are the increased serum hepcidin in CKD patients, so the stored iron in reticuloendothelial cells can't be used.[6]

Hepcidin is an essential regulatory protein, controlling intestinal iron absorption and iron distribution throughout the body, and it is the primary regulator of iron metabolism.[7] High-circulating hepcidin reduces iron absorption in response to oral or intravenous (IV) iron. It's secretion is done mainly by liver and the β- cells of the pancreas,it controls iron absorption from intestine and thus manage the iron stores in the body.[8] Hypoglycemia stimulates hepcidin formation and is released by pancreatic β-cells.[9] It is believed that iron overload occurs in hepcidin deficiency, increasing β-cell apoptosis.[10] Inflammatory responses happen in the early phase of CKD, manifesting by releasing pro-inflammatory cytokines, acute phase reactants, and hepcidin in CKD patients.[11] Hepcidin formation and secretion are affected by many factors, including hypoxia, anemia, serum erythropoietin (EPO), transferrin saturation, and liver iron load in CKD patients.[12] It was reported that stimulation of erythropoiesis by EPO hormone (EPO-H) decreases serum hepcidin, enhancing iron absorption, mobilization, and utilization.[13] Hypoxia is not uncommon in CKD patients. Hypoxia reduces serum hepcidin via hypoxia-inducible factor (HIF).[14] HIF works as a transcriptional activator to sense and adapt the cellular response to oxygen availability. Hypoxia directly affects intestinal iron absorption. Anemic hypoxia stimulates the hypoxia HIF/hypoxia response element (HRE) system. Hydroxylase enzyme activity reduces hypoxic status, leading to HIF-1α building with HIF-1β, presenting the HRE to the target gene promoters. Similarly, the stability of HIF-2α is affected by the partial pressure of oxygen via the altered activity of prolyl hydroxylase. HIF-2α has a role in hypoxic EPO expression signals.[15] HIF system is a negative modulator for hepcidin, stimulates erythropoiesis, and increases iron utilization. Furthermore, hypoxia downregulates hepcidin and induces oxidative stress, diminishing hepcidin expression.[16,17] Idris et al reported that in patients of CKD in

type 2 diabetes mellitus,most common type of anemia is normocytic normochromic.[18] The anemia is mainly due to the reduction in EPO-H synthesis by the kidneys and/or poor response to EPO-H. Iron is essential in cell metabolism, also required for oxygen transportation by Hb.[19]

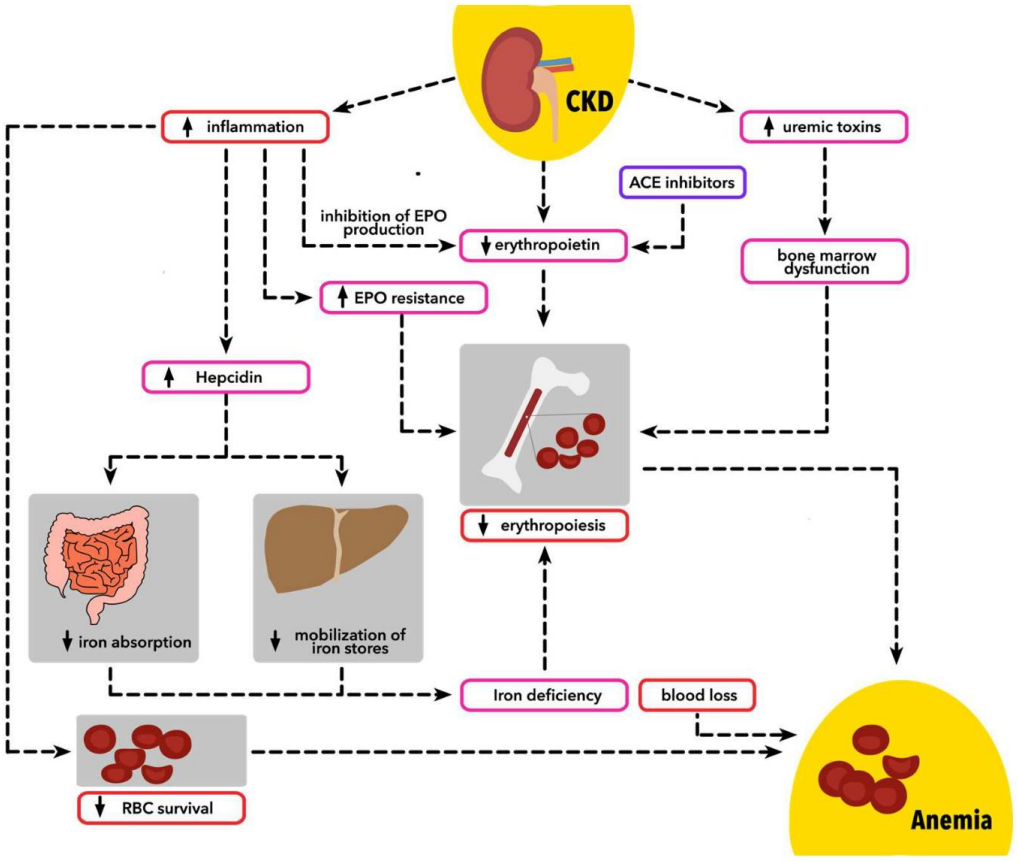

Figure 1: Pathophysiology of anemia in CKD.CKD chronic kidney disease;EPO—erythropoietin;ACE—angiotensin converting enzyme; RBC—red blood cells.[4]

CKD associated anemia, was initially used to be treated with blood transfusions, and was associated with complications like infections, transfusion reactions, hemosiderosis and fluid overload etc.[20,21] Darbepoetin alfa and recombinant human erythropoietin are two erythropoiesis-stimulating agents , used mainly in the treatment of anemia in CKD patients. They are almost similar in side effect and efficacy profile, except for less dosing frequency in darbepoetin alfa due to it's longer half life.[22,23]

Many patients with CKD don't respond to erythropoiein. Factors leading to unresponsiveness include inflammation and iron deficiency .Raised CRP levels predict erythropoietin resistance in patients on dialysis. To enhance erythropoietin responsiveness, iron supplements are recommended.[24]

Iron supplementation is required for almost all CKD patients having anemia. According to guidelines, intravenous (i.v.) iron supplementation is preferred method in CKD 5D patients and either oral or iv iron is recommended for patients with CKD stages 3–5 ND .[25]

Oral iron is usually the first line treatment for IDA, but some patients need the intravenous iron as the preferred option when oral iron is not effective or not tolerated, limited absorption, lack of adherence, intolerance or insufficient [13,14]. Intravenous iron may help improve iron correction with better adherence, fewer visit to the medical practitioner and greater convenience.[26]

Iron isomaltoside is a novel IV iron used in CKD patients with anemia .It has various advantages over traditional IV iron preparations, making it a better option for clinicians treating CKD patients with anemia. Iron isomaltoside consists of iron and isomaltoside in such a structure, which allows for a slow and controlled release of iron.[27] This unique composition contributes to its favorable pharmacokinetic profile and low risk of toxicity of free iron. The controlled release mechanism enables the use of single higher doses compared to other IV iron formulations, potentially reducing the number of hospital visits for iron replenishment.[28] Iron isomaltoside is found to be efficacious in treating IDA in CKD patients, both in dialysis and non dialysis patients .[29]

One of the key advantages of iron isomaltoside is its safety profile. The incidence of adverse events, particularly hypersensitivity reactions, appears to be lower compared to some other IV iron

formulations.[30] This is useful in CKD patients having multiple comorbidities. The improved safety profile allow for relatively more flexible dosing strategies and potentially reduce test dose requirements, which are usually needed with other IV iron preparations.

The ability to administer iron isomaltoside in high single doses (up to 20 mg/kg body weight) offers potential benefits in terms of patient convenience and healthcare resource utilization. Fewer hospital visits also reduce the overall cost of care.[27]

IS (iron sucrose) is a well-established intravenous (IV) iron formulation being used widely because of its efficacy, safety profile, and extensive clinical experience. Iron sucrose consists of a complex of polynuclear iron (III)-hydroxide in sucrose, with an average molecular weight of approximately 34,000-60,000 daltons.[31] This structure allows for controlled release of iron, which is then taken up by the reticuloendothelial system and subsequently incorporated into hemoglobin and other iron-containing proteins.[32]Its use is particularly important in patients not able to tolerate or respond adequately to iron supplements given orally , which is common in CKD due to reduced absorption and increased iron requirements.[33] Iron sucrose is also known to decrease the requirement for erythropoiesis- stimulating agents (ESAs) in CKD patients.[34]

Compared to older IV iron formulations, iron sucrose has a lower risk of anaphylactic reactions and other serious adverse events.[35]

In hemodialysis patients, iron sucrose is valuable in maintaining stores of iron and managing anemia. Regular administration of iron sucrose is well known for effectively maintaining stores of iron and hemoglobin levels.[36]

The dosing of IS (iron sucrose) in CKD patients involves frequent and smaller doses compared to some newer IV iron formulations. This requires more frequent hospital visits.[37]

Previous studies demonstrated good efficacy and safety profile of iron isomaltoside in different CKD populations. However, the safety and efficacy of iron sucrose versus iron isomaltoside on iron deficiency anemia is not established. This study was conducted to compare the efficacy as well as safety of iron isomaltoside and iron sucrose in patients of anemia in CKD stage 3-5 ND.

AIM AND OBJECTIVES

● To compare the safety profile of iron isomaltoside versus iron sucrose in patients of anemia in chronic kidney disease stage 3-5 ND.

● To compare the efficacy profile of iron isomaltoside versus iron sucrose in patients of anemia in chronic kidney disease stage 3-5 ND.

REVIEW OF LITERATURE

Iron deficiency is a major factor in the development of anemia in chronic kidney disease (CKD). For this reason, treating iron deficiency is essential to effectively managing anemia in CKD patients, especially in those who require renal replacement therapy.[38]

Patients with CKD who have been identified with iron shortage can replenish their iron stores with intravenous or oral iron treatments. Most of the time, the aims of therapy, tolerability, convenience, and response to previous therapy determine which agent to use. Iron deficiency anemia must be treated with IV iron formulations due to decreased absorption of iron in the gastrointestinal tract and a high rate of gastrointestinal side effects, which can reduce the effectiveness of oral iron agents. This is more important in patients requiring kidney replacement therapy. If kidney replacement therapy is not necessary, newer oral medications may address iron shortage and get over these restrictions. More aggressive iron replacement therapy may help treat anemia and improve key clinical outcomes including cardiovascular disease and survival in patients with CKD who require kidney replacement therapy, according to recent research. [39]

The studies conducted to assess the safety and effectiveness profile of iron sucrose vs iron isomaltoside in individuals with anemia in stages 3-5 of chronic renal disease are included below.

The physicochemical characteristics of iron isomaltoside 1000 (Monofer) and the intravenous iron preparations that are already on the market were compared by Jahn MR et al in 2011[40]. In contrast to iron isomaltoside 1000 (Monofer), the items under investigation include low molecular weight iron dextran (CosmoFer), sodium ferric gluconate (Ferrlecit), iron sucrose (Venofer), iron carboxymaltose (Ferinject/Injectafer), and ferumoxytol (Feraheme). It was

demonstrated that labile iron formulations such as sodium ferric gluconate , iron sucrose and stable polynuclear formulations such as iron dextran, iron carboxymaltose, ferumoxytol, and iron isomaltoside 1000 differ significantly and clinically.Their immunogenic capacity, safety, and ease of use—the latter demonstrated by the possibility of high single-dose administration and quick infusion times—all differ from one another. A novel parenteral iron product, Monofer has a very low amount of free and labile iron and a very low immunogenic potential. This means that Monofer, the only IV iron formulation available, can be given without the need for a test dose in a rapid high dose infusion at levels more than 1000 mg. This allows for a great deal of dose flexibility, including the potential to deliver one-dose iron repletion—complete iron replacement in a single infusion.

In 2011, Wikstrom B et al.[41] studied individuals with stage 5D CKD or NDD-CKD.Patients were either iron naive or prepared to switch their usual IV iron therapy. The creation of a safety profile for iron isomaltoside in patients with CKD was the main goal; effectiveness was the secondary goal. A total of 584 treatments with single doses up to 1,800 mg were administered, including 17 IV boluses of 100–200 mg, 523 IV boluses of 100 mg, and 44 high-dose infusions. Significant increases were seen in hemoglobin, transferrin saturation, and ferritin; no acute hypersensitivity reaction or delayed allergic responses were observed. It was determined that iron isomaltoside, when given to patients with CKD either as a single high-dose infusion or as repeated bolus injections, was well tolerated and improved anemia and iron status markers.

Patients with stage 3 and 4 CKD and IDA were randomly randomized by Agarwal R et al. in 2016[42] to receive either oral ferrous sulfate (325 mg three times daily for eight weeks) or intravenous iron sucrose (67 patients receiving 200 mg every two weeks, total 1 g). The main result was the variation in the slope of the two-year change in the measured glomerular filtration rate (mGFR) across the groups.19

patients in the oral iron treatment group and 17 participants in the intravenous iron group experienced 36 and 55 major cardiovascular events, respectively (adjusted incidence rate ratio 2.51 (1.56-4.04)). Hospitalization-related infections exhibited a noteworthy adjusted incidence rate ratio of 2.12 (1.24-3.64). Therefore, intravenous iron therapy is linked to a higher risk of major adverse events, such as those from cardiovascular causes and infectious infections, among non-dialyzed individuals with CKD and IDA.

New intravenous (IV) iron preparations should ideally be able to deliver a wide dosing range to allow iron correction in a single or low number of visits, a rapid infusion (doses up to 1,000 mg must be administered over more than 15 minutes, and doses exceeding 1,000 mg must be administered over 30 minutes or more), and minimal potential side effects, such as low catalytic/labile iron release with minimal risk of anaphylaxis, according to Kalra PA and Bhandari S[27] 2016 review, "Efficacy and safety of iron isomaltoside (Monofer®) in the management of patients with iron deficiency anemia. Iron isomaltoside (Monofer®) was developed with the purpose of meeting these needs. Comparing iron isomaltoside to a placebo, intravenous iron sucrose, and oral iron, it has been demonstrated to be efficacious in treating iron deficiency anemia in a variety of therapeutic patient groups. Iron and a carbohydrate moiety that are firmly bonded in a matrix structure make up iron isomaltoside. In addition to having a poor potential to produce labile iron and a low immunogenic potential, it doesn't seem to be linked to clinically severe hypophosphatemia. Iron isomaltoside has been shown in clinical trials and observational studies to be a safe, effective, and well-tolerated treatment for anemia in a variety of therapeutic domains.

The effectiveness and safety of iron isomaltoside, also referred to as ferric derisomaltose, and iron sucrose were compared by Derman R et al in 2017[29] in patients with IDA who were intolerant of or unresponsive to oral iron. The trial was a multi-center, comparative,

open-label study, 511 IDA patients with varying causes were observed for five weeks after being randomly assigned 2:1 to receive iron sucrose or iron isomaltoside. Hemoglobin (Hb) and body weight were used to calculate the total iron isomaltoside dose, which was given as a 500 mg injection over two minutes or a 1000 mg infusion over more than fifteen minutes. Ganzoni's formula was used to determine the total iron sucrose dose, which was then given as several 200 mg infusions spaced 30 minutes apart. The average cumulative dose of iron sucrose was 1127.9 mg and iron isomaltoside was 1640.2 mg. The primary end point was % individuals with a Hb rise by at least 2 g/dL from baseline at any point between weeks 1– 5. For the primary endpoint, both non-inferiority and superiority were validated, and iron isomaltoside was associated with a shorter time to Hb increase ≥2 g/dL. Iron isomaltoside was proven to increase biochemical efficacy metrics faster and/or more significantly. Despite a notable adverse drug event occurring in 0.6% of patients, both treatments were well tolerated. Iron isomaltoside was a more effective hemoglobin stabilizer than iron sucrose. The fact that iron isomaltoside can be given in fewer doses with a higher cumulative dose gives it an advantage over iron sucrose. Many IDA patients responded favorably to both drugs.

In order to compare the long term safety of FCM vs oral iron, Roger SD et al. conducted a study in 2017[43]. The study, which involved 616 individuals, discovered that the FCM groups experienced less adverse effects than the oral iron group did. Between groups, there was no significant difference in the frequency of infections, heart problems, or major adverse events. Ferritin levels ≥800 µg/L were observed in a small number of patients in the high ferritin FCM group; however, these results were not linked to an increase in adverse events or to stopping the study medication. In every group, the estimated glomerular filtration rate did not change. The findings bollster the safety of IV FCM in treating iron deficient anemia in CKD patients who are not reliant on dialysis. The study addresses the need for more thorough IV iron therapy safety data.

In 2019[44], Auerbach M et al. assessed the effectiveness and safety of iron sucrose (IS) and IIM in a large group of IDA patients. This multicenter, randomized, open-label, comparative study was carried out in the United States of America. The IDA patients were randomized 2:1 to receive iron sucrose (IS) as 200 mg intravenous injections as a single dose of 1000 mg IIM, up to five times. Adjudicated significant or severe hypersensitivity responses and hemoglobin change from baseline to week eight were the co-primary outcomes. There were 1512 patients enrolled in total. In the IIM group, the frequency of patients experiencing severe or major hypersensitivity responses was 0.3% (95% confidence interval: 0.06;0.88), while this was 0.4% (0.05;1.45) in the IS group. There was no discernible risk difference between the groups and the co-primary safety aim was satisfied. The co-primary efficacy objective of hemoglobin change non-inferiority was achieved and in the first two weeks, IIM produced a noticeably faster hematological response. In the IS group, the frequency of cardiovascular events was 1.2%, whereas in the IIM group it was 0.8%. In both groups, hypophosphatemia was uncommon. When 1000 mg of iron isomaltoside was delivered, the hematological reaction was more immediate and more significant than when IS was used, which necessitated numerous visits. With a low frequency of hypersensitive responses and cardiovascular events, the safety profile was comparable.

In a HD cohort, Mikhail AI et al. in 2019[45] evaluated the iron isomaltoside (IIM) 5% (Diafer®) therapy regimen, efficacy, and safety. In this prospective observational study, 198 HD patients receiving treatment with IIM in accordance with the product label and clinical protocol were switched from iron sucrose (IS). At three-month intervals, historical data for IS and data for IIM were compared. The primary endpoint was to demonstrate that IS and IIM are not inferior in terms of maintaining hemoglobin (Hb). The majority of patients (> 60%) adhered to a set low-dose iron treatment regimen. The administration of IIM and its preparation took three minutes. In both the IIM and IS

phases, erythropoiesis-stimulating agent (ESA) was administered to over 80% of patients. The mean Hb level was 11 g/dL, and the mean change of 0.3 g/dL (95% confidence interval: 0.1, 0.5) for IIM 0–3 months compared to IS proved non-inferiority. The maintenance of Hb was similar with both iron medications. In 2% of the patients who received IIM, nine adverse medication responses were recorded. Every patient recovered without incident. When comparing IS to IIM, the frequency of metallic taste was higher. They came to the conclusion that IIM is safe and effective for CKD patients on HD. In terms of Hb maintenance, IIM and IS were comparable in terms of ESA requirements. The low frequency of metallic taste adds to patient convenience, and the fast-push injection of IIM may facilitate logistical improvements in clinical practice.

An extensive review of the treatment of iron deficiency (ID) and iron deficiency anemia (IDA) was published in 2019[46] by Ning S and Zeller MP. Steps outlined by the authors were: iron replenishment, underlying etiology inquiry. Serum ferritin was the principal test utilized for diagnosis; in inflammatory situations, transferrin saturation was employed as a marker. Increased iron requirements, malabsorption, and blood loss are among the causes of ID. it was concluded that ,while many individuals found oral iron to be affordable, gastrointestinal side effects were frequently reported.Rapid repletion was seen with high-dose IV iron formulations.

A retrospective observational study was carried out in 2020 by Jesus-Silva JA et al[47] in two centers with the aim of comparing the safety and effectiveness of iron sucrose (IS-Venofer®) vs iron isomaltoside (IIM-Diafer®) in patients undergoing hemodialysis. Patients who were receiving Venofer and on dialysis at the time of the trial were transferred to Diafer® and followed up for a minimum of 12 months for each iron preparation. The mean age of the 190 patients who were included was 65.8 years. Over a 12-month period, there was no change in the mean hemoglobin per milligram of iron supplied,

confirming non-inferiority. During the study period, there was no significant difference in the number of reported adverse events between the 41,295 prescriptions for iron isomaltoside and the 14,685 prescriptions for iron sucrose. There was a statistically significant impact on Hb over time, even when multiple comparisons were taken into account. Ferritin showed notable improvements with time, staying at six months. After modification, the weekly iron dosage remained the same. Patients who transitioned to IIM did not have a significant difference in the EPO dose . They came to the conclusion that there is no difference in the quantity of reported adverse events when it comes to iron isomaltoside and iron sucrose's ability to sustain hemoglobin levels in patients undergoing routine hemodialysis or hemofiltration.

Using information from prospective clinical trials, Pollock RF & Biggar P compared ferric derisomaltose (FDI), iron sucrose (IS), and ferric carboxymaltose (FCM) in 2020[48]. Using standardized MedDRA queries (SMQs), hypersensitivity reactions (HSRs) classified as significant or severe, were the focus of the analysis. The researchers used techniques for indirect treatment comparison, naïve pooling, and Bayesian inference. The findings demonstrated that, across all analytic methodologies, FDI was linked to reduced risks of significant or severe HSRs than FCM and IS. Data from 21 prospective trials, totaling over 8,000 patients, were included in the study. The authors draw the conclusion that a thorough comparison of HSR incidence amongst the three IV iron products was made possible by the use of SMQ-coded safety data from prospective studies. They suggest that in order to aid in the synthesis of evidence, future randomized controlled trials record HSRs using the SMQ paradigm.

In 2020[49], Kalra PA et al. assessed the effect of high-versus low-dose intravenous iron isomaltoside on the likelihood that patients with iron-deficient non-diabetic kidney disease (ND-CKD) will retreat with intravenous iron. In this prospective, real-world observational investigation, 256 ND-CKD patients receiving anemia treatment in the

UK provided data. After receiving iron isomaltoside for the first time, patients were monitored for at least 12 months. The investigators made the decision about the iron dosage and if retreatment was necessary. The main goal of the trial was to determine if patients who got more than 1000 mg of iron during Course 1 or those who received less than 1000 mg needed to retreat at 52 weeks.Adverse medication reactions were used to assess safety. At Week 52, the >1000 mg iron group (n = 58) had a significantly reduced chance of retreatment than the ≤1000 mg group (n = 198). Other blood and iron parameter changes did not differ substantially between the two groups. Giving more than 1000 mg of iron Compared to ≤1000 mg, isomaltoside saved 8.6 appointments for every 100 patients. There were no reports of any severe adverse medication responses. They came to the conclusion that, in comparison to the ≤1000 mg regimen, the >1000 mg iron isomaltoside regimen decreased the likelihood of retreatment, produced a higher hemoglobin response independent of erythropoiesis stimulating agent treatment and decreased the overall number of appointments needed.

The safety and effectiveness of a single infusion of FDI 1,000 mg versus up to five doses of iron sucrose (IS) 200 mg (recommended cumulative dose, 1,000 mg) over an 8-week period were assessed in a randomized, open-label, multi-center clinical trial carried out in 2021 by Ambrosy AP et al[50] in patients with NDD-CKD and iron deficiency anemia. 244 (16%) of the 1,525 patients that were included of the safety analysis had a history of heart failure (HF). Overall, there was little difference in the rate of acute or severe hypersensitivity events between treatments groups. Cardiovascular adverse events (AEs) were documented in 4.2 % of patients without heart failure and 9.4% of patients with HF. Following FDI administration, the time to the first cardiovascular adverse event (AE) was longer than it was with IS; this difference held true for patients with or without heart failure. Patients that received FDI as opposed to IS experienced a quicker hematological response, as indicated by shifts in hemoglobin and

ferritin concentrations as well as an increase in transferrin saturation. In summary, compared to numerous doses of IS, a single infusion of FDI was found to be safe, well-tolerated, and related with fewer cardiovascular adverse events (AEs) and a faster hematological response in patients with NDD-CKD. Both HF patients and non HF patients experienced similar effects.

In 2021, Bhandari S et al.[51] assessed iron isomaltoside's safety and effectiveness. Patients were randomized 2:1 to receive either a single dosage of 1000 mg IIM or iron sucrose (IS) provided as 200 mg IV injections up to five times during a two-week period in this randomized, open-label, multi-center experiment carried out in the USA. Serious or severe hypersensitivity reactions and changes in hemoglobin (Hb) from baseline to Week 8 were the co-primary outcomes. The frequency of composite cardiovascular adverse events (AEs) was one of the secondary objectives. With a mean estimated glomerular filtration rate of 35.5 mL/min/1.73 m2, 1538 individuals in total were included. Since there was no discernible difference in the incidence of major or severe hypersensitivity responses between the IIM and IS groups, the coprimary safety objective was satisfied. Composite cardiovascular adverse events (AEs) were substantially less common in the IIM group than in the IS group. In comparison to IS, IIM caused a more noticeable rise in Hb during the first four weeks. The co-primary efficacy goal was achieved, as evidenced by the non-inferiority of the change in Hb by Week 8. One dose of IIM produced a non-inferior 8-week haematological response, relatively low rates of hypersensitivity responses, and a significantly reduced incidence of composite cardiovascular adverse events (AEs) when compared to numerous doses of IS.

According to Lee KH et al. in 2021[52], iron therapy was essential for controlling anemia in patients with chronic kidney disease (CKD). Because of their low absorption and gastrointestinal side effects, traditional oral iron supplements had little efficacy. Improved

bioavailability and tolerance were provided by more recent oral iron formulations, such as sucrosomial iron, heme iron polypeptide, ferric citrate, and ferric maltol. Because it also worked as a phosphate binder, ferric citrate is special. Intravenous iron stays crucial, particularly for hemodialysis patients, as newer formulations make it possible to administer larger dosages more quickly.

In 2022[53], Chen T et al. carried out a meta analysis and systematic review to assess the safety and effectiveness of intravenous iron supplementation at varying frequency in patients suffering from renal anemia. Up until September 17, 2021, the authors searched through several databases for randomized controlled trials (RCTs).Transferrin saturation (TSAT), serum ferritin (SF), and hemoglobin (HGB) were evaluated as efficacy indicators, and safety outcomes such allergies, i nfections, cardiovascular events, and all cause mortality were evaluated. In terms of TSAT, SF, and HGB, the study did not show any significant differences between the low-frequency high dose (12 doses, >200 mg/dose) and high-frequency low dose (4 doses, ≤200 mg/dose) groups. Likewise, no statistically significant dose variations were discovered in safety outcomes, including cardiovascular events, allergies, infections and overall death from all causes. In individuals suffering from CKD associated anemia, the safety and effectiveness characteristics of the dosages are similar. They did point out that intravenous iron administered in one or two doses might be more affordable and more tolerable for patients.

In 2023[54], Shi L et al. carried out a meta-analysis to investigate the impact of iron sucrose against iron isomaltoside ferumoxytol on iron deficient anemia. Through March 2021, they examined the databases of the Cochrane Library, EMbase, Web of Science, EBSCO, and PubMed for randomized controlled trials (RCTs) evaluating the impact of iron sucrose against iron isomaltoside ferumoxytol on iron deficiency anemia. The random-effect model was utilized in the meta-analysis process. Inclusion of four RCTs with 3892 patients in the meta-

analysis. Overall, iron isomaltoside for iron deficiency anemia shown comparable changes in hemoglobin, serum ferritin, and transferrin saturation when compared to iron sucrose. Iron sucrose did not, however, improve serum ferritin as much as iron isomaltoside did at week two. They came to the conclusion that iron isomaltoside ferumoxytol and iron sucrose were equally effective in treating iron deficient anemia.

In 2023[55], Kassianides X and Bhandari S studied about a secondary analysis of a randomized controlled trial that looked at how intravenous iron treatment affected cardiovascular markers and patient-reported outcomes in patients with iron deficiency and non-dialysis dependent chronic kidney disease (ND-CKD). The research involved assigning 26 patients, at random, to receive ferric carboxymaltose or ferric derisomaltose. Prior to and following therapy, researchers evaluated cardiac indicators, fatigue, functional status, and quality of life. The majority of quality of life domains, tiredness state, and functional capacity improved similarly with both iron formulations, according to the results. Cardiac indicators did not change, nor did arterial stiffness. The authors draw the conclusion that intravenous iron therapy may improve the functional status and quality of life of ND-CKD patients without appearing to carry any short-term cardiovascular hazards. Iron isomaltoside's efficacy, safety, and tolerability were examined by Biggar P et al[56] in the treatment of iron deficiency anemia (IDA) in 698 patients with chronic renal failure, including those on dialysis and those with stages 3-5 non dialysis chronic kidney disease (CKD). Hemoglobin (Hb), hematocrit, iron, transferrin saturation (TSAT), and ferritin were measured for effectiveness at baseline, three months, and nine months. Adverse events and safety laboratory indicators were measured for safety. The average hemoglobin level rose from 11.0 g/dL to 11.6 g/dL, TSAT increased from 19.4% to 28.3%, and ferritin increased from 320 µg/L to 642 µg/L following a mean cumulative dose of 2,574 mg isomaltoside during a 9-month period, indicating improved iron deficiency. Furthermore, a noteworthy decrease in the utilization of

erythropoiesis-stimulating agents (ESAs) was seen, as the dosage of epoetin - α dropped from 40,688 IU/month to 35,665 IU/month (-13.7%, $p < 0.001$). There were no documented drug-related side effects, and phosphate and other safety metrics indicated no unusual changes. According to the study's findings, iron isomaltoside showed excellent efficacy and tolerability in patients with stage 3-5 CKD, as well as the ability to save ESA.

In a 56-week open-label, multicenter, prospective randomized trial, Macdougall IC et al. in 2014[57] examined the best course of iron therapy for 626 non-dialysis-dependent patients with chronic kidney disease (CKD) who had iron deficiency and anemia but were not on erythropoiesis-stimulating agents (ESAs).Patients were randomized (1:1:2) to either oral iron therapy or intravenous (IV) ferric carboxymaltose (FCM), which targets ferritin levels 400–600 µg/L or 100–200 µg/L. The time to start alternative anemia management or the haemoglobin (Hb) trigger of two consecutive values <10 g/dL during Weeks 8–52 was the primary outcome. Findings indicated that in the groups receiving oral iron, low-ferritin FCM, and high-ferritin FCM, the primary endpoint was experienced by 23.5%, 32.2%, and 31.8% of patients, respectively (hazard ratio: 0.65; 95% CI: 0.44-0.95; P = 0.026 for high-ferritin FCM versus oral iron).

The best way to supplement iron for anemia in patients with progressive renal insufficiency (PRI) , not yet receiving dialysis was examined by Stoves J et al. [58] in their study. Forty-five patients were randomly assigned to receive concurrent erythropoietin (rHuEpo) treatment and either intravenous iron (300 mg iron sucrose weekly) or oral iron (ferrous sulphate 200 mg tds). While red cell hypochromasia alterations and hemoglobin responses were similar in both groups throughout an average follow-up of 5.2 months, the intravenous group's serum ferritin level was considerably greater. Iron sucrose may have caused allergic responses in three people. In 43% of patients receiving oral iron and 33% of those receiving intravenous iron (NS),

the rHuEpo dose may be temporarily stopped, with final doses of 33.5 (0-66) and 41.6 (0-124) U/kg/week, respectively (NS). Oral iron was associated with a higher frequency of moderate gastrointestinal symptoms .The study found that, in terms of hemoglobin response and rHuEpo dose requirements, monthly 300 mg IV iron sucrose did not outperform daily 600 mg oral ferrous sulphate in pre-dialysis patients.

In 2018[59], Auerbach M et al. carried out a study on IV iron. Of the 1512 individuals who were enrolled in the trial, 26% had gastrointestinal bleeding and 50% had gynecologic bleeding. A single 1000 mg dosage of iron isomaltoside or several 200 mg doses of iron sucrose were administered to the patients in a 2:1 randomization. The main outcomes were changes in hemoglobin (Hb) from week 8 to baseline and hypersensitivity episodes. The outcomes demonstrated comparable safety profiles for both therapies, with minimal incidences of significant adverse drug reactions, cardiovascular events, and hypersensitivity reactions. During the first two weeks, iron isomaltoside caused a markedly faster and higher Hb response and showed no inferiority in Hb change. Additionally, it led to quicker responses in serum ferritin and transferrin saturation as well as greater improvements in FACIT fatigue scores at week 1. According to the study's findings, iron isomaltoside 1000, when taken as a single 1000 mg dose, had a similar safety profile to iron sucrose but produced a quicker and more noticeable hematological reaction as well as an improvement in fatigue.

MATERIALS AND METHODS

SOURCE OF DATA: Source of data was patients of CKD stage 3-5 ND
STUDY DESIGN: A prospective comparative study

Investigations (Hb, serum ferritin, transferrin saturation)
Base line
At 2 weeks
At 4 weeks
At 8 weeks

Adverse drug reactions (Rash, Pruritus, acute myocardial infarction, Drug hypersensitivity, Infusion related reaction)

SAMPLING: Random.

7.2 METHOD OF COLLECTION OF DATA

This prospective comparative study was done in DMCH Ludhiana . The study included 100 patients divided into two groups of 50 each. Group 1 received a 1000mg single dose of iron isomaltoside given over 20 minutes, while Group 2 received iron sucrose in 200mg IV injections (five times) over two weeks, for a total dose of 1000mg. The study duration was 10 weeks, including at least six visits per patient . Hb, serum iron and TSAT was compared at 2^{nd} ,4^{th} and 8^{th} week between two groups.

INCLUSION CRITERIA

- Men or women ≥18 years.
- Haemoglobin ≤11 g/dL
- Transferrin saturation <20%
- Serum ferritin <100 ng/ml

Chronic kidney disease ND, as defined by CKD- Epi - eGFR<60 ml /min//1.73m2 (not on dialysis)

EXCLUSION CRITERIA

- Haemochromatosis or other iron storage disorders.
- Known hypersensitivity reaction to any component of IIM and IS or previous serious hypersensitivity reactions to any intravenous iron compounds.
- During 10-day period prior to screening; if treated with intravenous iron.
- During 30-day period prior to screening or during the trial period; had been or would be treated with a red blood cell transfusion, radiotherapy, and/or chemotherapy.
- Undergoing dialysis for treatment of chronic kidney disease or under consideration for dialysis during the trial period.
- Any lab abnormality, psychiatric or medical condition ehich would put the patient's disease management at risk or might result in the patient being unable to comply with the trial requirements.

DURATION OF STUDY/NUMBER OF CASES: Duration of study was 10 Weeks (Including 14 days screening period) and total 100 patients with anemia in CKD stage 3-5 (ND) were taken.

OUTCOME

Safety (Adverse drug reaction) and efficacy (Haematological response) of iron isomaltoside VERSUS iron sucrose.

STATISTICAL ANALYSIS

When applicable, the range, mean, +/- standard deviation (SD), frequencies (number of cases), and relative frequencies (percentages) were used to characterize any pertinent data. The Mann Whitney test was used to compare quantitative variables between the research groups. An exact test and the Chi-square(X) test were employed to compare categorical data. It was determined that a probability value (p-value) of less than 0.05 was statistically significant. The statistical software SPSS 21 (Statistical Package for the Social Science) for Microsoft Winds was used to do all statistical computations.

OBSERVATION AND RESULTS

This prospective comparative study aimed to evaluate the safety and efficacy of iron isomaltoside versus iron sucrose in patients with chronic kidney disease (CKD) stage 3-5 with anemia. The study included 100 patients randomized into two groups of 50 each. Group 1 received a single 1000mg dose of iron isomaltoside infused over 20 minutes, while Group 2 received iron sucrose in 200mg IV injections up to five times over two weeks, for a cumulative dose of 1000mg. The study duration was 10 weeks, including a 14-day screening period, with at least six visits per patient.

Table 1- Summary of baseline anemia parameters and demographics

		Group 1		Group 2		Chi-square value	p-value
		No. of cases/mean	%age/SD	No. of cases/mean	%age/SD		
Age group	< 40	5	10.0%	6	12.0%	0.457	0.978
	41-50	3	6.0%	4	8.0%		
	51-60	18	36.0%	16	32.0%		
	61-70	18	36.0%	17	34.0%		
	> 70	6	12.0%	7	14.0%		
AGE		57.80	12.38	57.50	11.80	-0.093	0.926
GENDER	F	19	38.0%	26	52.0%	1.98	0.159
	M	31	62.0%	24	48.0%		
CKD STAGE	3	7	14.0%	5	10.0%	0.410	0.815
	4	18	36.0%	18	36.0%		
	5	25	50.0%	27	54.0%		
BMI		30.02	1.55	29.68	2.05	-1.524	0.128
CREATININE		4.47	1.92	4.52	1.78	-0.231	0.817
eGFR		18.90	19.16	14.66	7.73	-1.063	0.288
DM		25	50.0%	23	46.0%	0.160	0.841
ESA		35	70.0%	37	74.0%	0.198	0.824
HYPERSENSITIVITY REACTION RASH		0	0.0%	0	0.0%	0.000	1.000
PRURITUS		0	0.0%	1	2.0%	1.010	0.315
FEVER		1	2.0%	2	4.0%	0.344	0.558
ADVERSE EFFECTS_ACTUE MI		0	0.0%	0	0.0%	0.000	1.000
INCREASE_2ND WEEK_HB	< 1	50	100.0%	50	100.0%	0.000	1.000
INCREASE_4TH WEEK_HB	< 1	39	78.0%	49	98.0%	9.47	0.004
	>=1	11	22.0%	1	2.0%		
INCREASE_8THWEEK_HB	< 1	5	10.0%	25	50.0%	19.048	0.001
	>=1	45	90.0%	25	50.0%		
TSAT 20-50	N	3	6.0%	12	24.0%	6.353	0.023
	Y	47	94.0%	38	76.0%		
S.FERRITIN > 100	< 100	1	2.0%	19	38.0%	20.25	0.001
	> 100	49	98.0%	31	62.0%		
Total		50	100.0%	50	100.0%		

Table 2- Change in Hb (g/dl), TSAT (%) and Ferritin (ng/mL) from baseline to week 2, 4 and 8

	Group 1		Group 2		Z	p-value
	Mean	SD	Mean	SD		
BASELINE_HB	7.47	1.08	7.51	1.28	-0.086	0.931
2ND WEEK_HB	7.85	1.09	7.77	1.28	-0.348	0.728
4TH WEEK_HB	8.30	1.10	8.05	1.28	-0.876	0.381
8THWEEK_HB	8.74	1.06	8.49	1.29	-0.869	0.385
DIFF 2ND WEEK_HB	-0.39	0.16	-0.26	0.12	-5.095	0.001
DIFF 4TH WEEK_HB	-0.83	0.20	-0.54	0.13	-6.960	0.001
DIFF 8THWEEK_HB	-1.28	0.42	-0.99	0.17	-6.127	0.001
BASELINE_TSAT	10.28	4.45	10.64	4.55	-0.627	0.530
2ND WEEK_TSAT	15.64	5.95	14.07	4.64	-0.907	0.364
4TH WEEK_TSAT	22.83	7.65	18.38	5.61	-2.677	0.007
8THWEEK_TSAT	31.83	9.73	23.70	6.77	-4.304	0.001
DIFF 2ND WEEK_TSAT	-5.37	3.44	-3.43	1.94	-2.710	0.007
DIFF 4TH WEEK_TSAT	-12.55	5.90	-7.74	3.95	-4.471	0.001
DIFF 8THWEEK_TSAT	-21.55	7.91	-13.06	5.26	-5.805	0.001
BASELINE_FERRITIN	62.29	29.10	51.85	32.94	-1.482	0.138
2ND WEEK_FERRITIN	108.03	36.71	68.81	49.04	-5.009	0.001
4TH WEEK_FERRITIN	156.78	47.69	84.68	52.76	-6.177	0.001
8THWEEK_FERRITIN	212.66	50.85	135.43	68.73	-5.923	0.001
DIFF 2ND WEEK_FERRITIN	-45.73	27.04	-16.96	31.39	-6.611	0.001
DIFF 4TH WEEK_FERRITIN	-94.49	38.92	-32.83	36.05	-7.190	0.001
DIFF 8THWEEK_FERRITIN	-150.37	44.89	-83.58	62.68	-6.087	0.001

Table 3: Distribution of patients in different age-groups in the two treatment groups

		Group 1		Group 2		Total	Chi-square value	p-value
		No. of cases	%age	No. of cases	%age			
Age group	< 40	5	10.0%	6	12.0%	11	0.457	0.978
	41-50	3	6.0%	4	8.0%	7		
	51-60	18	36.0%	16	32.0%	34		
	61-70	18	36.0%	17	34.0%	35		
	> 70	6	12.0%	7	14.0%	13		
Total		50	100.0%	50	100.0%	100		

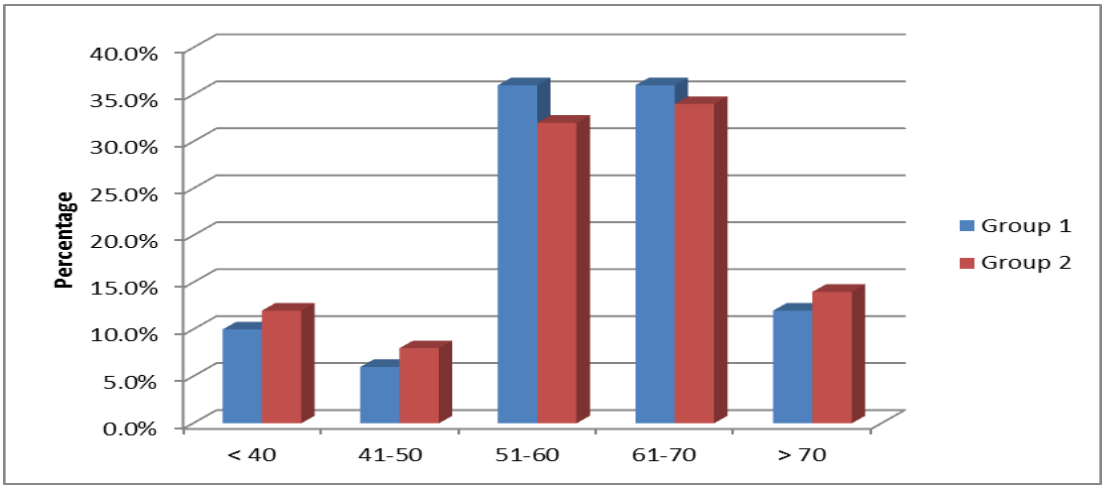

Figure 2: Distribution of patients in different age-groups in the two treatment groups

The above table compares the age distribution of patients in two treatment groups. The distribution was fairly similar between the two groups, with the majority of patients falling in the 51-60 and 61-70 age ranges for both groups. Group 1 had slightly more patients in these middle age ranges, while Group 2 had slightly more in the youngest and oldest categories, but these differences were minor. The chi-square value of 0.457 and p-value of 0.978 indicated that there was no statistically significant difference in age distribution between the two groups.

Table 4: Mean age

	Group 1		Group 2		Z	p-value	Difference		95% Confidence Interval of the Difference	
	Mean	SD	Mean	SD			Mean	Std. Error	Lower	Upper
AGE	57.80	12.38	57.50	11.80	-0.093	0.926	0.30	2.42	-4.50	5.10

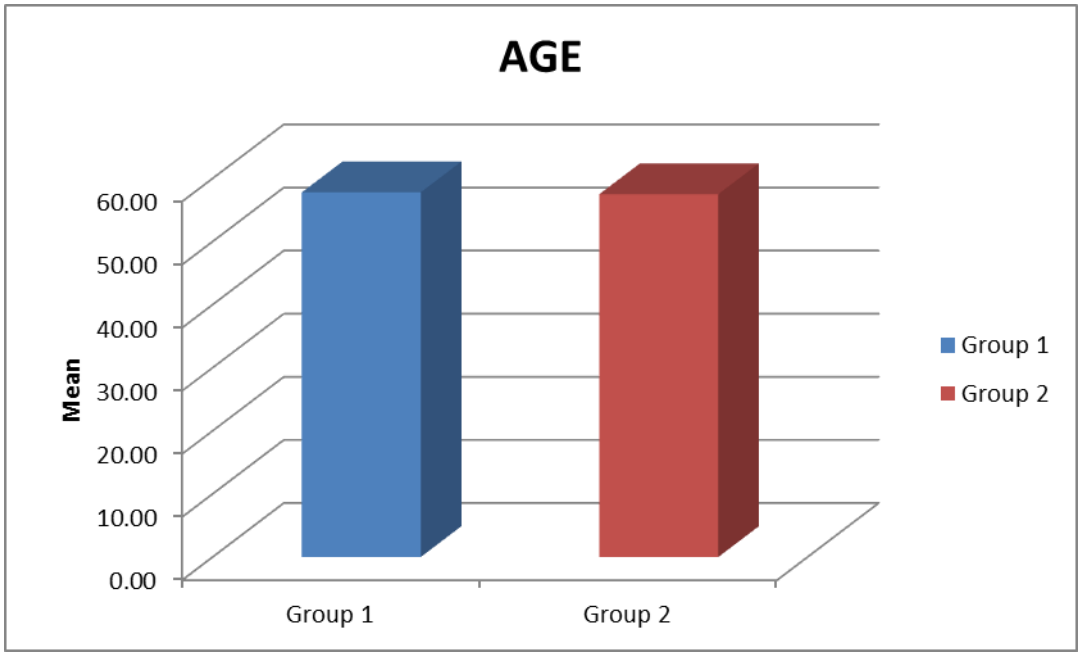

Figure 3: Mean age

Group 1 had a mean age of 57.80 years with a standard deviation of 12.38, while Group 2 had a mean age of 57.50 years with a standard deviation of 11.80. The statistical analysis showed a Z-score of -0.093 and a p-value of 0.926, indicating no significant difference in age between the groups. The mean difference was 0.30 years with a standard error of 2.42. The 95% confidence interval for this difference ranges from -4.50 to 5.10 years.

Table 5: Gender wise distribution of patients in the two treatment groups

		Group 1		Group 2		Total	Chi-square value	p-value
		No. of cases	%age	No. of cases	%age			
GENDER	F	19	38.0%	26	52.0%	45	1.98	0.159
	M	31	62.0%	24	48.0%	55		
Total		50	100.0%	50	100.0%	100		

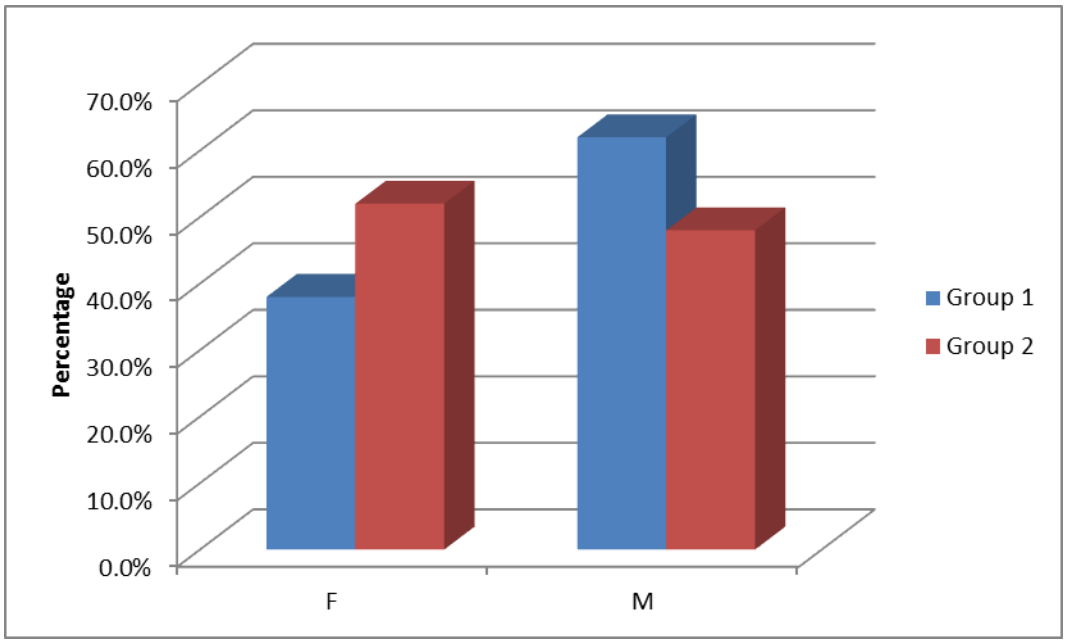

Figure 4: Gender wise distribution of patients in the two treatment groups

The above table presents the gender distribution across two groups. Group 1 consisted of 19 females (38%) and 31 males (62%), while Group 2 had 26 females (52%) and 24 males (48%), totaling 100 participants. Group 1 had a higher proportion of males, while Group 2 had a slightly higher proportion of females. The chi-square value of 1.98 and p-value of 0.159 indicated that this difference in gender distribution between the groups was not statistically significant.

Table 6: Comparison of Patient Characteristics and Renal Function Parameters among two groups

	Group 1		Group 2		Z	p-value	Difference		95% Confidence Interval of the Difference	
	Mean	SD	Mean	SD			Mean	Std. Error	Lower	Upper
BMI	30.02	1.55	29.68	2.05	-1.524	0.128	0.34	0.36	-0.38	1.06
CREATININE	4.47	1.92	4.52	1.78	-0.231	0.817	-0.05	0.37	-0.79	0.69
eGFR	18.90	19.16	14.66	7.73	-1.063	0.288	4.24	2.92	-1.56	10.04

The above table compares three clinical parameters (BMI, Creatinine, and eGFR) between two groups. Group 1 had slightly higher mean BMI (30.02 vs 29.68) and eGFR (18.90 vs 14.66), but lower mean Creatinine (4.47 vs 4.52) compared to Group 2. However, none of these differences were statistically significant, as indicated by the p-values all being greater than 0.05 (0.128 for BMI, 0.817 for Creatinine, and 0.288 for eGFR).

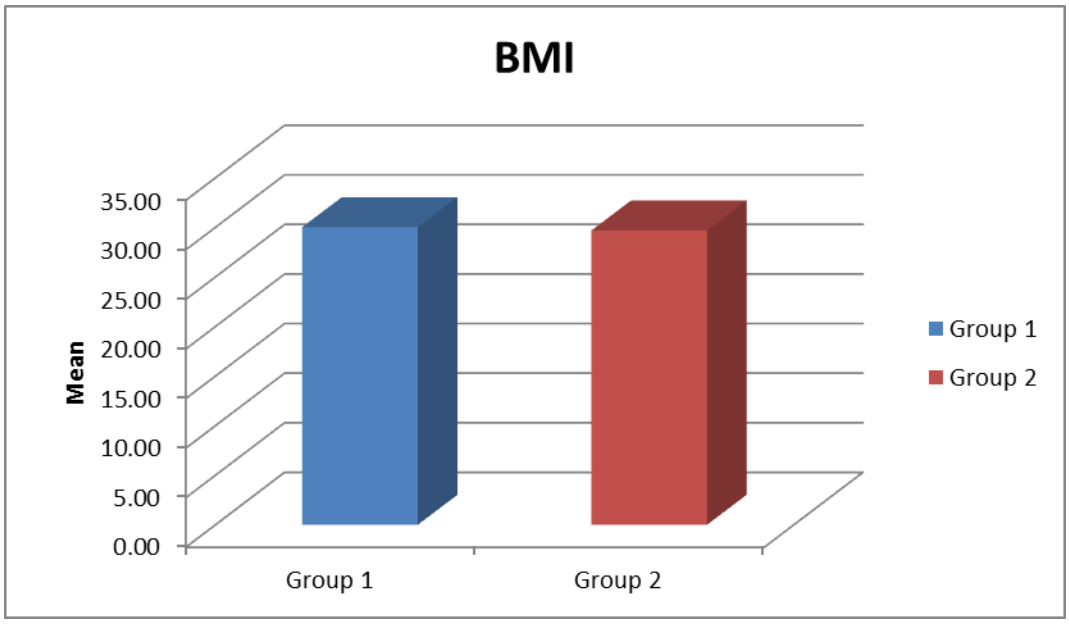

Figure 5.1: Comparison of Patient Characteristics and Renal Function Parameters among two groups

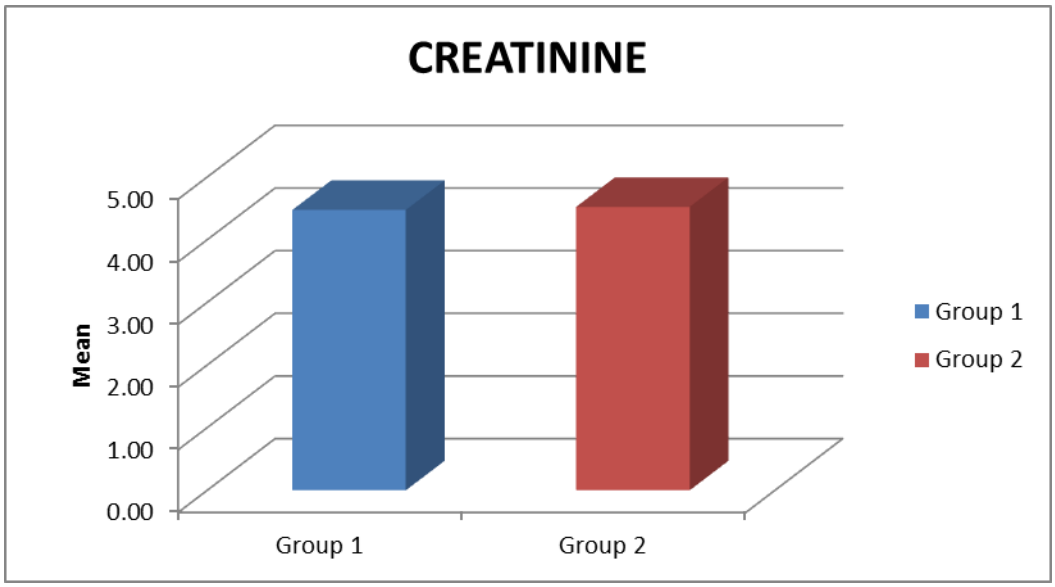

Figure 5.2: Comparison of Patient Characteristics and Renal Function Parameters among two groups

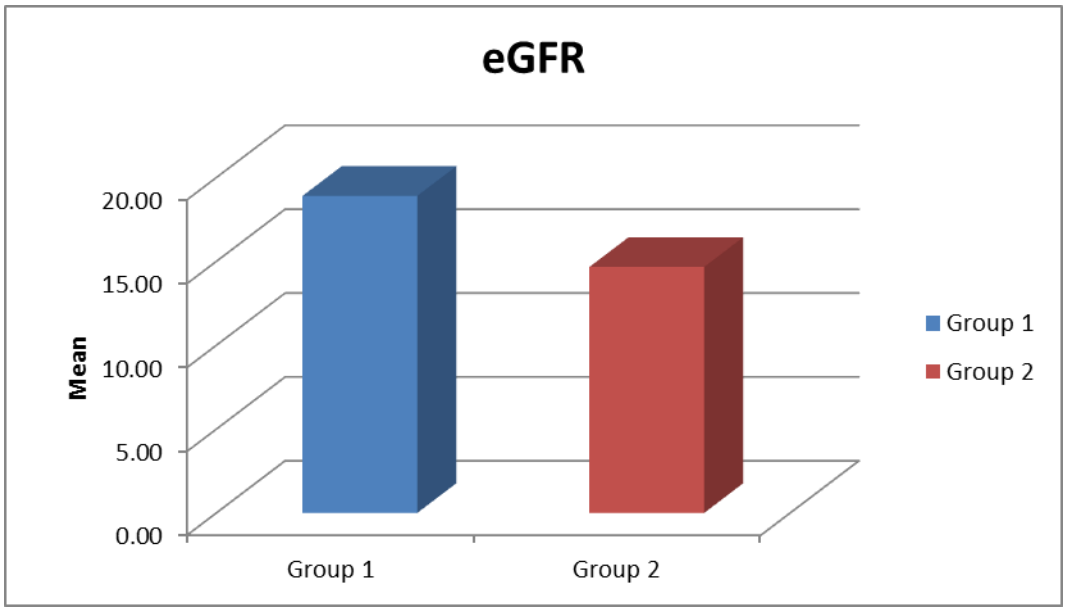

Figure 5.3: Comparison of Patient Characteristics and Renal Function Parameters among two groups

Table 7: Distribution of patients as per the stage of CKD in the two treatment groups

		Group 1		Group 2		Total	Chi-square value	p-value
		No. of cases	%age	No. of cases	.%age			
CKD TAGE	3	7	14.0%	5	10.0%	12	0.410	0.815
	4	18	36.0%	18	36.0%	36		
	5	25	50.0%	27	54.0%	52		
Total		50	100%	50	100%	100		

The above table compares the distribution of Chronic Kidney Disease (CKD) stages between two groups. Both groups showed a similar distribution across CKD stages 3, 4, and 5. In Group 1, 14% were in stage 3, 36% in stage 4, and 50% in stage 5. Group 2 had a slightly different distribution with 10% in stage 3, 36% in stage 4, and 54% in stage 5. The chi-square value of 0.410 and p-value of 0.815 indicated that these differences in CKD stage distribution between the groups were not statistically significant.

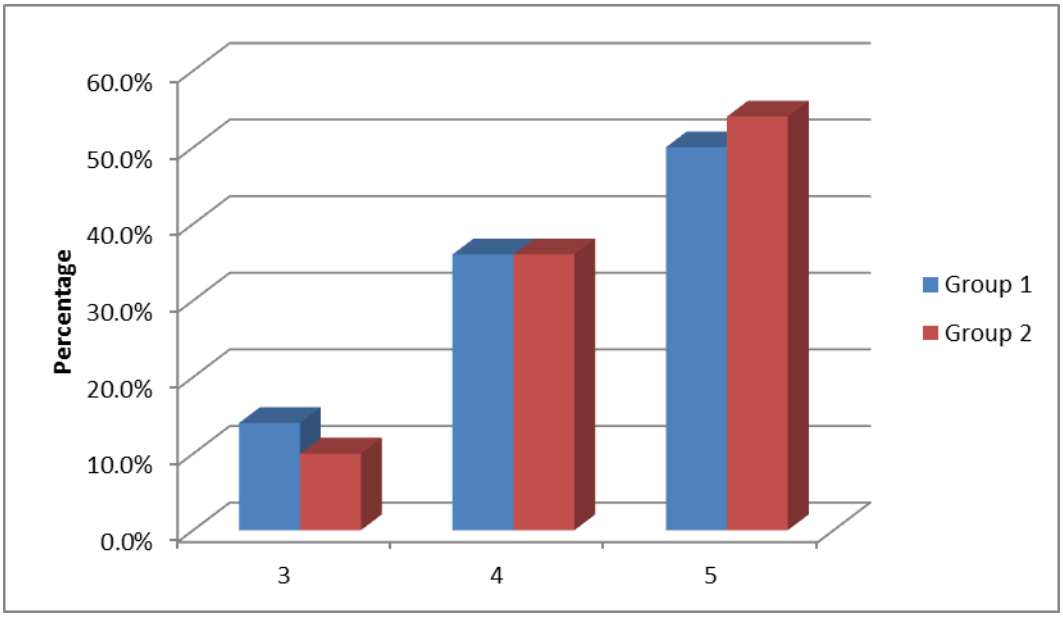

Figure 6: Distribution of patients as per the stage of CKD in the two treatment groups

Table 8: Comparison of Prevalence of Diabetes Mellitus and ESA Use among two groups

		Group 1		Group 2		Total	Chi-square value	p-value
		No. of cases	%age	No. of cases	%age			
DM	Y	25	50.0%	23	46.0%	48	0.160	0.841
ESA	Y	35	70.0%	37	74.0%	72	0.198	0.824

The above table compares the prevalence of two medical conditions or treatments between two groups. DM was present in 50% of Group 1 and 46% of Group 2. ESA was used in 70% of Group 1 and 74% of Group 2. The chi-square values (0.160 for DM and 0.198 for ESA) and corresponding p-values (0.841 for DM and 0.824 for ESA) indicate that these differences between the groups were not statistically significant.

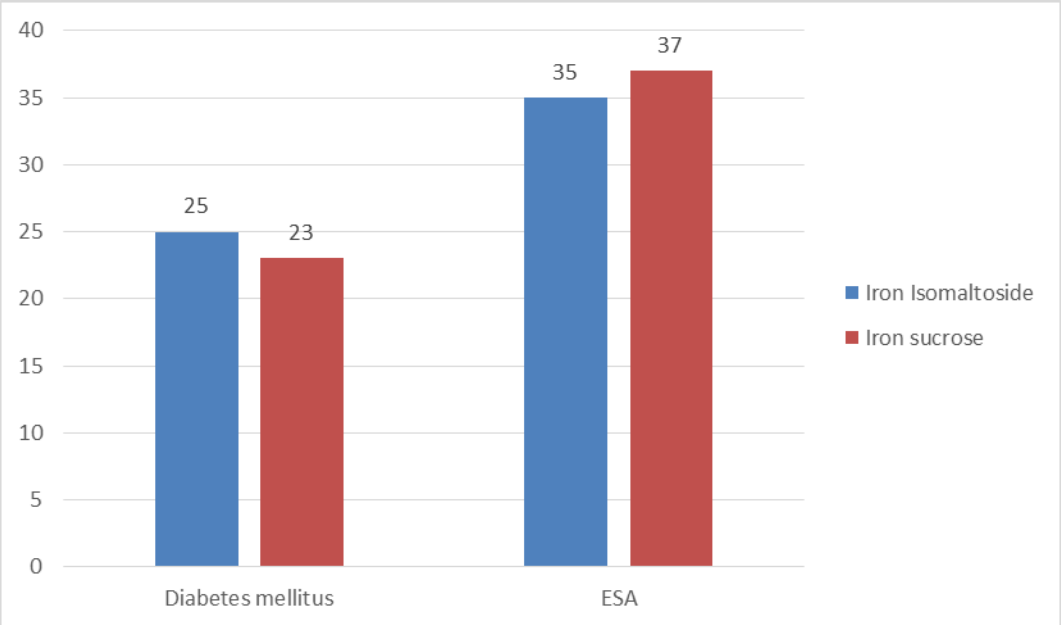

Figure 7: Comparison of Prevalence of Diabetes Mellitus and ESA Use among two groups

Table 9: Comparison of hypersensitivity reaction among two groups

HYPERSENSITIVITY REACTIONS		Group1		Group 2				
		No of cases	%age	No of cases	%age	total	Chi-square value	p-value
RASH	Y	0	0.0%	0	0.0%	0		
PRURITUS	Y	0	0.0%	1	2.0%	1	1.010	0.315
FEVER	Y	1	2.0%	2	4.0%	3	0.344	0.558
Total		50	100.0%	50	100.0%	100		

The above table compares the occurrence of hypersensitivity reactions between two groups of 50 patients each. Three types of reactions were reported: rash, pruritus, and fever. Rash did not occur in either group. Pruritus was observed in 0% of Group 1 and 2% (1 patient) of Group 2. Fever occurred in 2% (1 patient) of Group 1 and 4% (2 patients) of Group 2. The chi-square values and p-values (1.010 and 0.315 for pruritus; 0.344 and 0.558 for fever) indicated that these differences were not statistically significant.

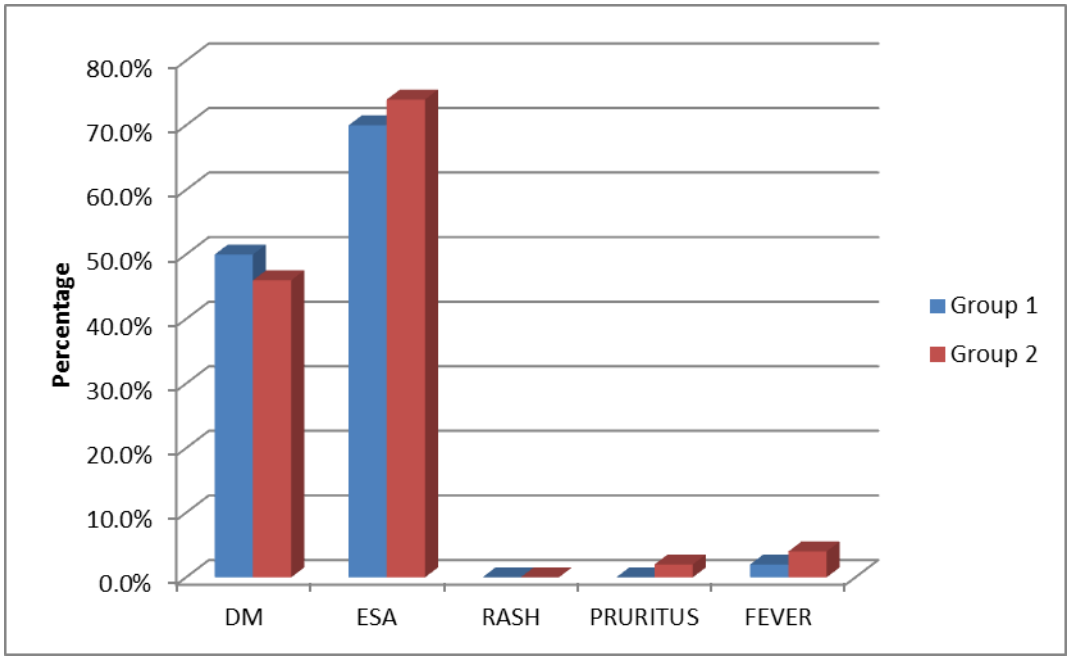

Figure 8: Comparison of hypersensitivity reaction among two groups

Table 10: Comparison of Adverse effects among two groups

		Group 1		Group 2		Total	Chi-square value	p-value
		No of cases	%age	No of cases	%age			
ADVERSE EFFECTS_ACTUE MI	N	50	100.0%	50	100.0%	100		
Total		50	100.0%	50	100.0%	100		

The above table compared two groups (Group 1 and Group 2) with respect to the occurrence of adverse effects, specifically acute myocardial infarction (MI). The table shows that 100% of participants in both groups didn't experience the adverse effect of acute MI.

Table 11: Comparison of Hb levels at baseline, 2nd, 4th and 8th week between two groups

	Group 1		Group 2		Z	p-value	Difference		95% Confidence Interval of the Difference	
	Mean	SD	Mean	SD			Mean	Std. Error	Lower	Upper
BASELINE_HB	7.47	1.08	7.51	1.28	-0.086	0.931	-0.04	0.24	-0.51	0.43
2ND WEEK_HB	7.85	1.09	7.77	1.28	-0.348	0.728	0.09	0.24	-0.39	0.56
4TH WEEK_HB	8.30	1.10	8.05	1.28	-0.876	0.381	0.25	0.24	-0.22	0.73
8THWEEK_HB	8.74	1.06	8.49	1.29	-0.869	0.385	0.25	0.24	-0.22	0.72

The above table presents a comparison of hemoglobin (Hb) levels between two groups over time, measured at baseline, 2nd week, 4th week, and 8th week. The data suggested a trend of increasing hemoglobin levels in both groups over time, with Group 1 showing slightly higher mean values at later time points. However, none of the comparisons reached statistical significance (all p-values > 0.05), indicating that the observed differences between the groups were not statistically meaningful.

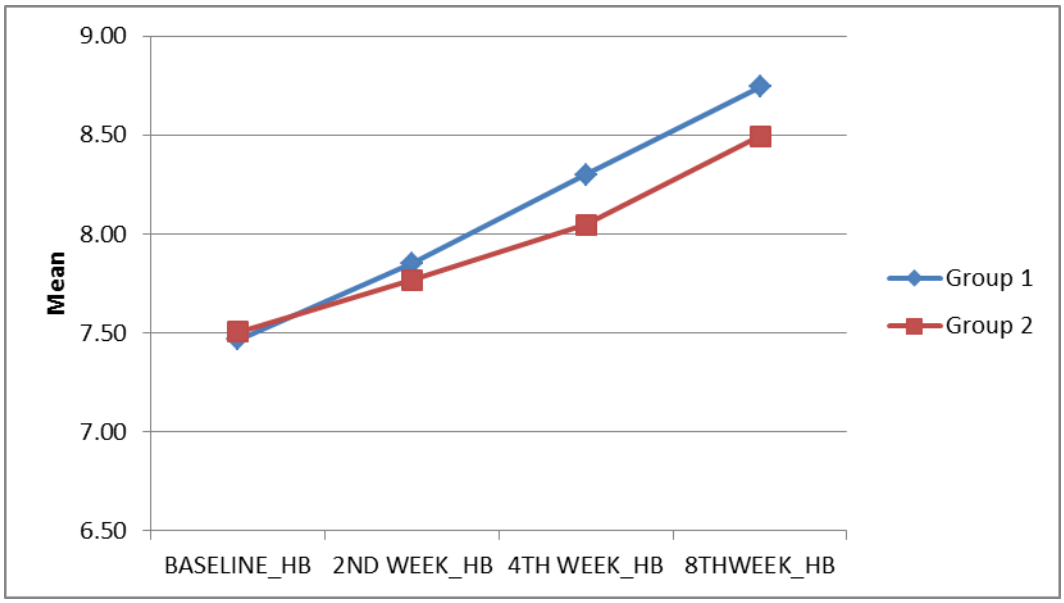

Figure 9: Comparison of HB levels at baseline,2nd, 4th and 8th week between two groups

Table 12: Comparison of Hemoglobin Differences between Group 1 and Group 2 at 2nd, 4th, and 8th Weeks

	Group 1		Group 2		Z	p-value	Difference		95% Confidence Interval of the Difference	
	Mean	SD	Mean	SD			Mean	Std. Error	Lower	Upper
DIFF 2ND WEEK_HB	-0.39	0.16	-0.26	0.12	-5.095	0.001	-0.13	0.03	-0.18	-0.07
DIFF 4TH WEEK_HB	-0.83	0.20	-0.54	0.13	-6.960	0.001	-0.29	0.03	-0.36	-0.23
DIFF 8THWEEK_HB	-1.28	0.42	-0.99	0.17	-6.127	0.001	-0.29	0.06	-0.42	-0.16

This table compares the changes in hemoglobin (HB) levels between two groups at different time points (2nd week, 4th week, and 8th week) relative to a baseline. Group 1 consistently showed larger increases compared to Group 2. The statistical analysis revealed significant differences between the groups at all time points, with p-values of 0.001 for each comparison. Specifically, by the 8th week, Group 1 had a mean increase of 1.28 g/dL in HB levels, while Group 2 had a mean increase of 0.99 g/dL, resulting in a statistically significant difference of 0.29 g/dL between the groups.

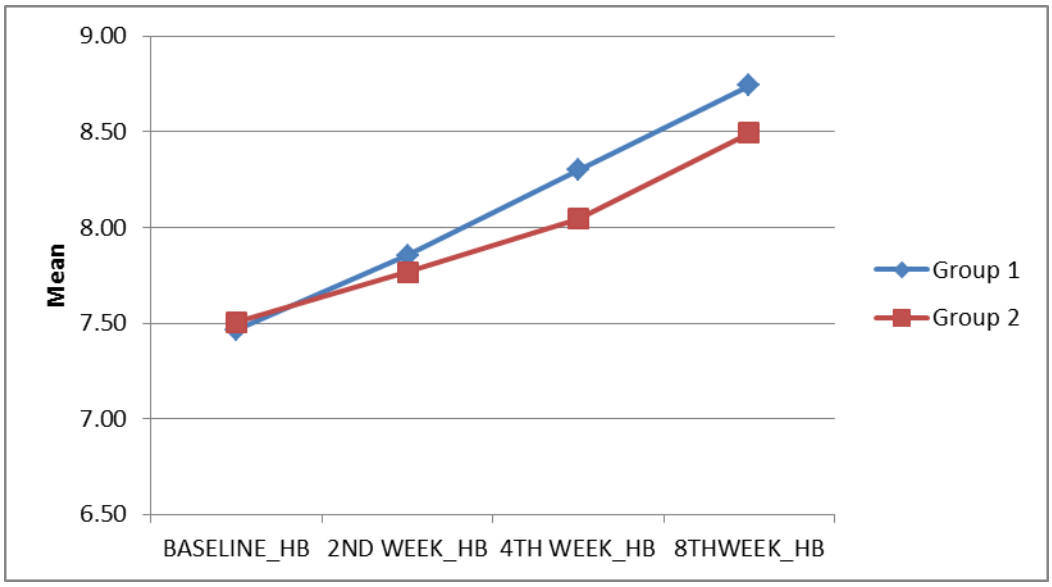

Figure 10: Comparison of Hemoglobin Differences between Group 1 and Group 2 at 2nd, 4th, and 8th Weeks

Table 13: Comparison of TSAT levels at baseline, 2nd, 4th and 8th week between two groups

	Group 1		Group 2		Z	p-value	Difference		95% Confidence Interval of the Difference	
	Mean	SD	Mean	SD			Mean	Std. Error	Lower	Upper
BASELINE_TSAT	10.28	4.45	10.64	4.55	-0.627	0.530	-0.36	0.90	-2.14	1.43
2ND WEEK_TSAT	15.64	5.95	14.07	4.64	-0.907	0.364	1.58	1.07	-0.54	3.70
4TH WEEK_TSAT	22.83	7.65	18.38	5.61	-2.677	0.007	4.45	1.34	1.79	7.11
8THWEEK_TSAT	31.83	9.73	23.70	6.77	-4.304	0.001	8.13	1.68	4.80	11.45

The above table compares transferrin saturation (TSAT) levels between two groups over time, measured at baseline, 2nd week, 4th week, and 8th week. Initially, both groups had similar TSAT levels (around 10%). As time progressed, both groups showed increases in TSAT, but Group 1 demonstrated larger increases. The differences became statistically significant at the 4th week (p=0.007) and 8th week (p=0.001).

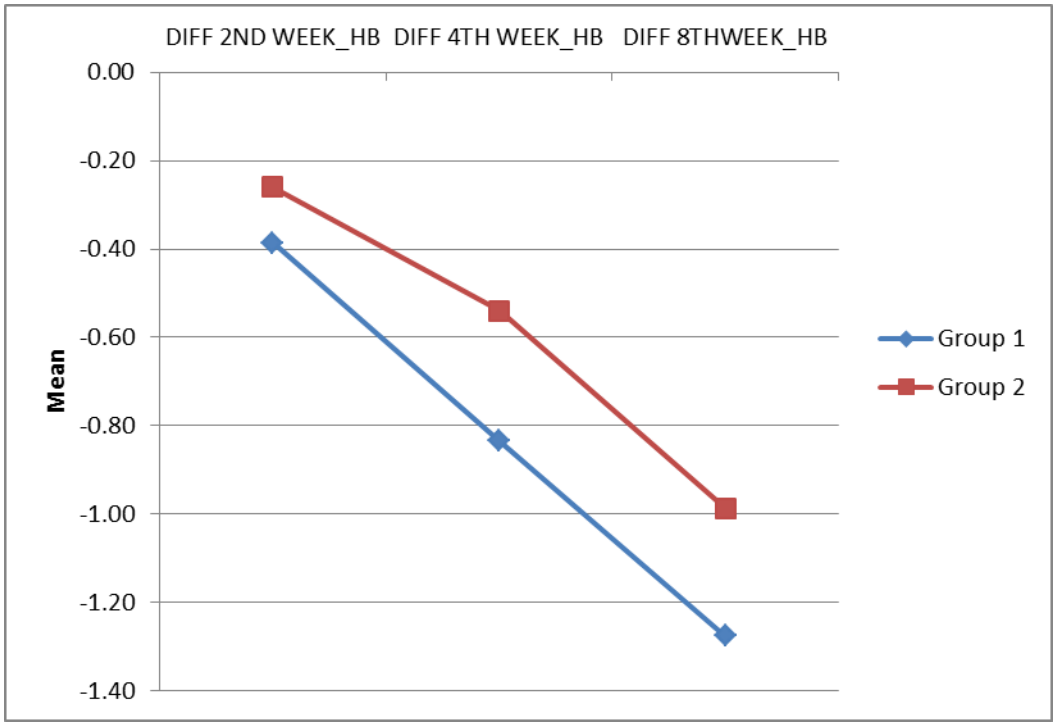

Figure 11: Comparison of TSAT levels at baseline, 2nd, 4th and 8th week between two groups

Table 14: Comparison of TSAT Differences between Group 1 and Group 2 at 2nd, 4th, and 8th Weeks

	Group 1		Group 2		Z	p-value	Difference		95% Confidence Interval of the Difference	
	Mean	SD	Mean	SD			Mean	Std. Error	Lower	Upper
DIFF 2ND WEEK_TSAT	-5.37	3.44	-3.43	1.94	-2.710	0.007	-1.93	0.56	-3.04	-0.83
DIFF 4TH WEEK_TSAT	-12.55	5.90	-7.74	3.95	-4.471	0.001	-4.81	1.00	-6.80	-2.81
DIFF 8THWEEK_TSAT	-21.55	7.91	-13.06	5.26	-5.805	0.001	-8.48	1.34	-11.15	-5.82

The above table compares the changes in transferrin saturation (TSAT) levels between two groups at 2nd week, 4th week, and 8th week relative to baseline. Group 1 consistently showed larger increases compared to Group 2. The differences between the groups were statistically significant at all time points (p=0.007 at 2nd week, p=0.001 at 4th and 8th weeks).

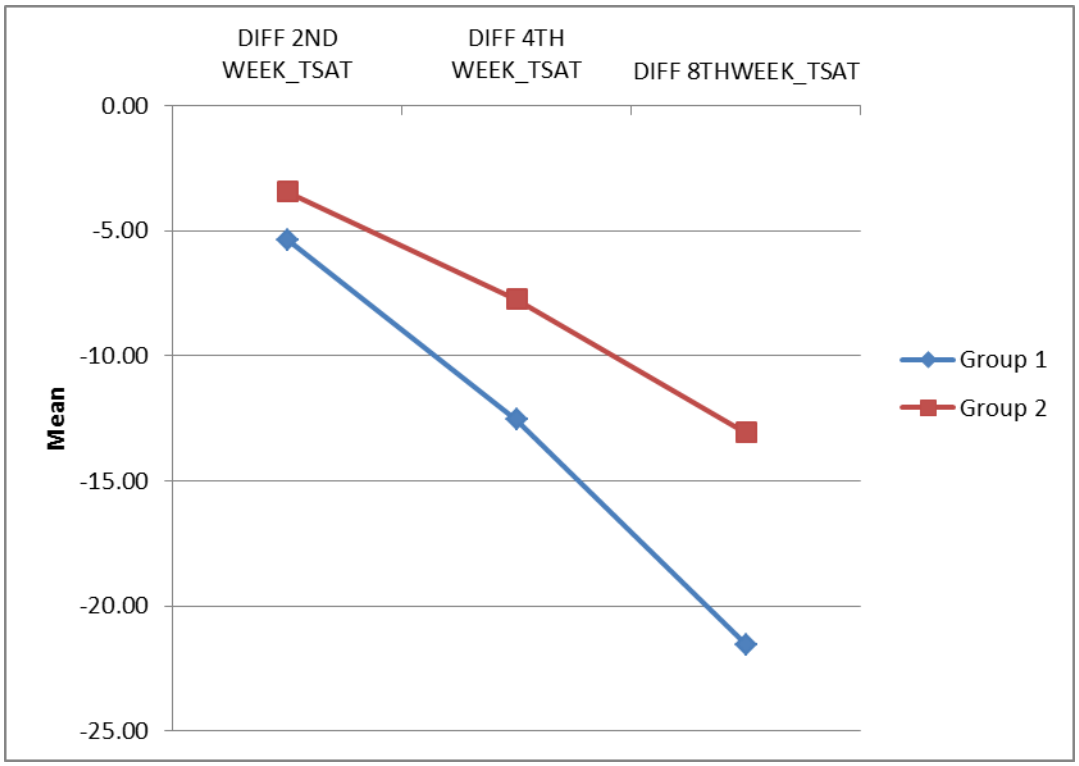

Figure 12: Comparison of TSAT Differences between Group 1 and Group 2 at 2nd, 4th, and 8th Weeks

Table 15: Comparison of ferritin levels at baseline, 2nd, 4th and 8th week between two groups

	Group 1		Group 2		Z	p-value	Difference		95% Confidence Interval of the Difference	
	Mean	SD	Mean	SD			Mean	Std. Error	Lower	Upper
BASELINE_FERRITIN	62.29	29.10	51.85	32.94	-1.482	0.138	10.44	6.22	-1.89	22.78
2ND WEEK_FERRITIN	108.03	36.71	68.81	49.04	-5.009	0.001	39.22	8.66	22.03	56.41
4TH WEEK_FERRITIN	156.78	47.69	84.68	52.76	-6.177	0.001	72.10	10.06	52.14	92.06
8THWEEK_FERRITIN	212.66	50.85	135.43	68.73	-5.923	0.001	77.23	12.09	53.24	101.23

This table compares ferritin levels between two groups over time, measured at baseline, 2nd week, 4th week, and 8th week. At baseline, there was no statistically significant difference between the groups (p=0.138). However, from the 2nd week onwards, Group 1 showed significantly higher ferritin levels compared to Group 2 (p=0.001 for all subsequent time points). The mean difference between the groups increased over time, from 39.22 ng/mL at the 2nd week to 77.23 ng/mL by the 8th week. Both groups experienced increases in ferritin levels throughout the study period, but Group 1's increase was more pronounced. By the 8th week, Group 1's mean ferritin level (212.66 ng/mL) was substantially higher than Group 2's (135.43 ng/mL).

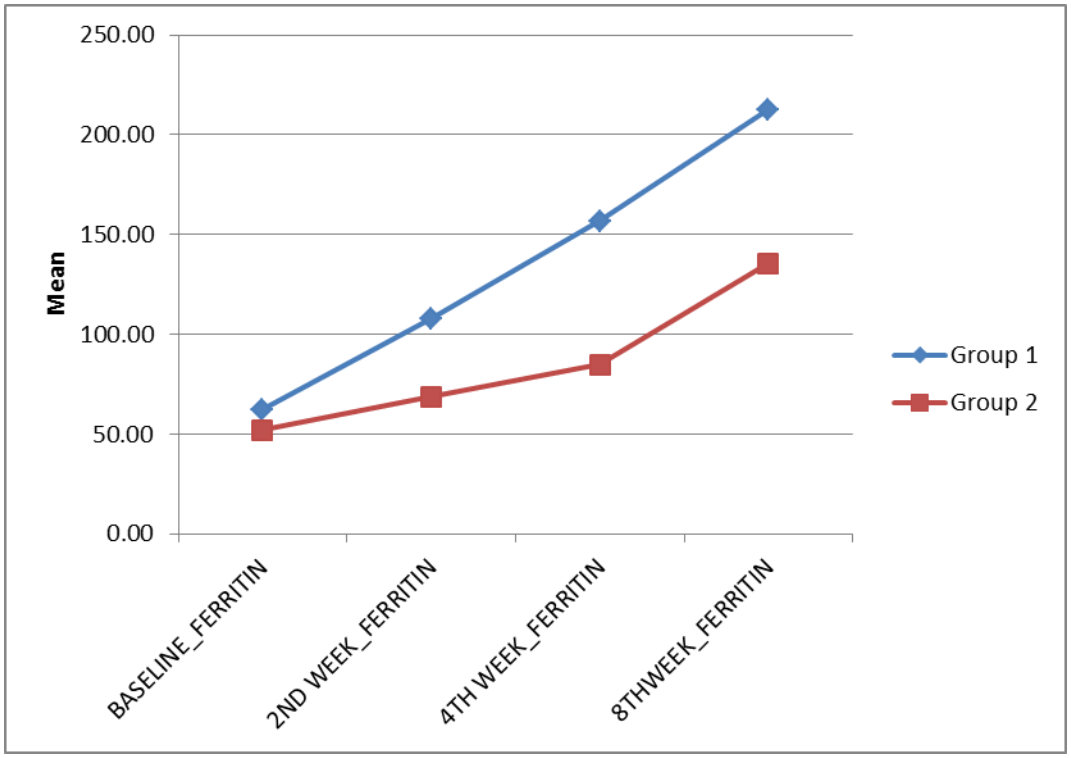

Figure 13: Comparison of ferritin levels at baseline, 2nd, 4th and 8th week between two groups

Table 16: Comparison of Ferritin differences between Group 1 and Group 2 at 2nd, 4th, and 8th Weeks

	Group 1		Group 2		Z	p-value	Difference		95% Confidence Interval of the Difference	
	Mean	SD	Mean	SD			Mean	Std. Error	Lower	Upper
DIFF 2ND WEEK_FERRITIN	-45.73	27.04	-16.96	31.39	-6.611	0.001	-28.78	5.86	-40.40	-17.15
DIFF 4TH WEEK_FERRITIN	-94.49	38.92	-32.83	36.05	-7.190	0.001	-61.66	7.50	-76.54	-46.77
DIFF 8THWEEK_FERRITIN	-150.37	44.89	-83.58	62.68	-6.087	0.001	-66.79	10.90	-88.43	-45.15

The table compares the changes in ferritin levels between two groups at 2nd week, 4th week, and 8th week relative to baseline. Group 1 consistently showed larger increases compared to Group 2. The differences between the groups were statistically significant at all time points (p=0.001 for all comparisons). By the 8th week, Group 1 had a mean increase of 150.37 ng/mL in ferritin levels, while Group 2 had a mean increase of 83.58 ng/mL, resulting in a statistically significant difference of 66.79 ng/mL. This suggested that the intervention or condition associated with Group 1 led to consistently greater improvements in iron storage, as indicated by larger increases in ferritin levels throughout the study period compared to Group 2.

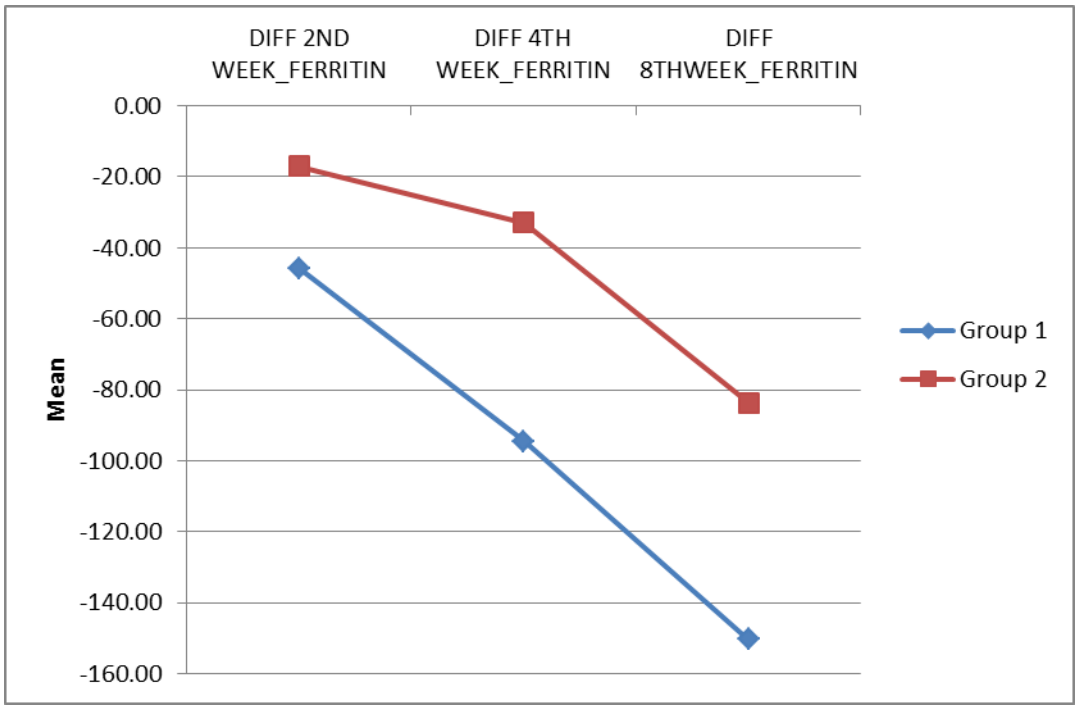

Figure 14: Comparison of Ferritin differences between Group 1 and Group 2 at 2nd, 4th, and 8th Weeks

Table 17: Comparison of hemoglobin increase between Group 1 and Group 2 at 2nd, 4th, and 8th Weeks

INCREASE_		Group 1		Group 2		Total	Chi-square value	p-value
		No. of Cases	%	No. of Cases	%			
2ND WEEK_Hb	< 1	50	100.0%	50	100.0%	100		
4TH WEEK_Hb	< 1	39	78.0%	49	98.0%	88	9.47	0.004
	>=1	11	22.0%	1	2.0%	12		
8THWEEK_Hb	< 1	5	10.0%	25	50.0%	30	19.048	0.001
	>=1	45	90.0%	25	50.0%	70		
Total		50	100.0%	50	100.0%	100		

The above table compares the increase in hemoglobin (Hb) levels between two groups at 2nd, 4th, and 8th weeks. At the 2nd week, all participants in both groups had an Hb increase of less than 1 g/dL. By the 4th week, a significant difference emerged (p=0.004), with 22% of Group 1 achieving an increase of ≥1 g/dL compared to only 2% in Group 2. The difference became more pronounced by the 8th week (p=0.001), where 90% of Group 1 had an Hb increase of ≥1 g/dL, compared to only 50% in Group 2. The chi-square values and p-values indicated that these differences were statistically significant, particularly at the 4th and 8th week time points.

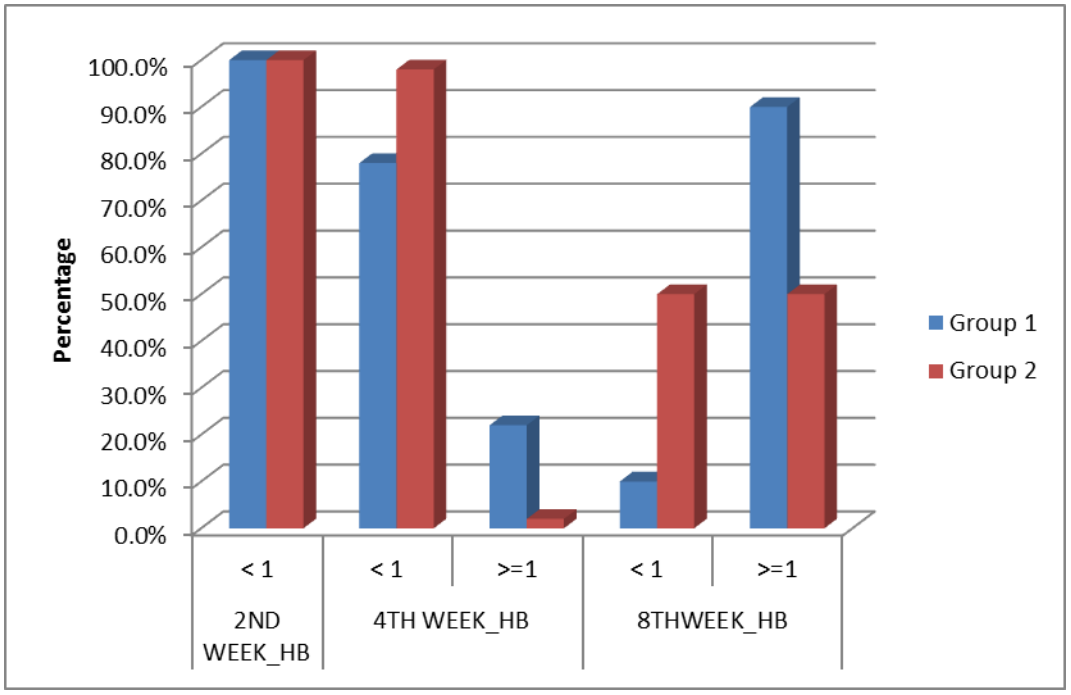

Figure 15: Comparison of hemoglobin increase between Group 1 and Group 2 at 2nd, 4th, and 8th Weeks

Table 18: Distribution of Patients with TSAT Levels 20-50% in Group 1 and Group 2

		Group 1		Group 2		Total	Chi-square value	p-value
		No of cases	%age	No of cases	%age			
TSAT 20-50	N	3	6.0%	12	24.0%	15	6.353	0.023
	Y	47	94.0%	38	76.0%	85		
Total		50	100.0%	50	100.0%	100		

The above table compares the achievement of a target transferrin saturation (TSAT) range of 20-50% between two groups. In Group 1, 94% of participants (47 out of 50) reached the target TSAT range, while in Group 2, 76% (38 out of 50) achieved this goal. Conversely, only 6% (3 out of 50) in Group 1 failed to reach the target range, compared to 24% (12 out of 50) in Group 2. The chi-square value of 6.353 and the p-value of 0.023 indicated that this difference between the groups was statistically significant.

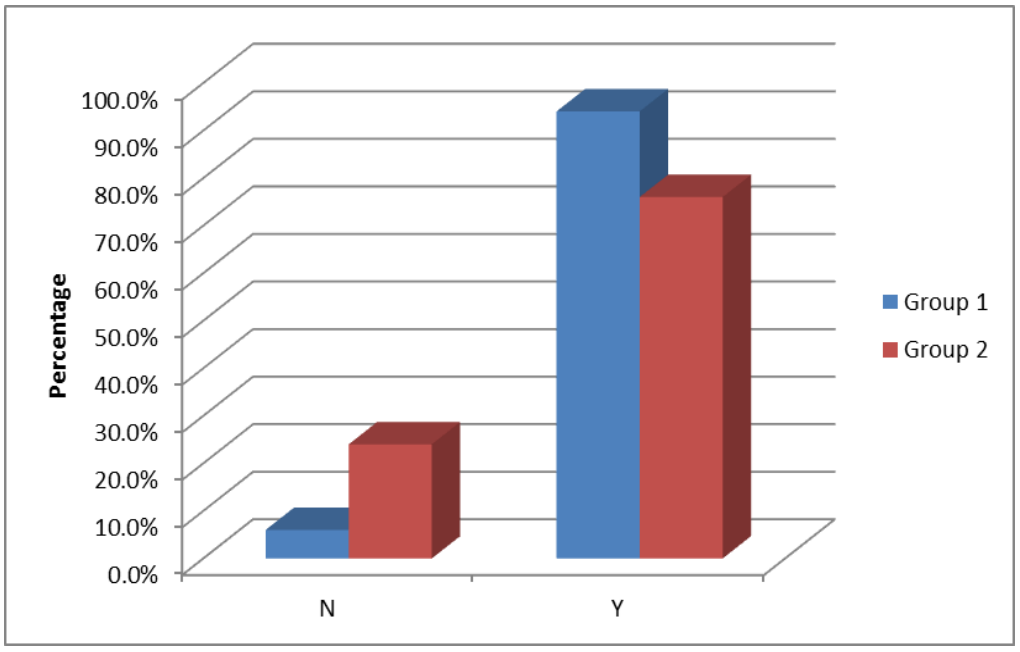

Figure 16: Distribution of Patients with TSAT Levels 20-50% in Group 1 and Group 2

Table 19: Distribution of Patients with Serum Ferritin Levels Above and below 100 ng/mL in Group 1 and Group 2

		Group 1		Group 2		Total	Chi-square value	p-value
		No of cases	%age	No of cases	%age			
S.FERRITIN > 100	< 100	1	2.0%	19	38.0%	20	20.25	0.001
	> 100	49	98.0%	31	62.0%	80		
Total		50	100%	50	100%	100		

The above table presents the comparison between two groups based on serum ferritin (S. Ferritin) levels, with a threshold of 100. Group 1 had 2% of individuals with ferritin levels below 100 and 98% with levels above 100, while Group 2 had 38% below 100 and 62% above 100. A Chi-square value of 20.25, with a p-value of 0.001, indicated a statistically significant difference in the distribution of ferritin levels between the two groups.

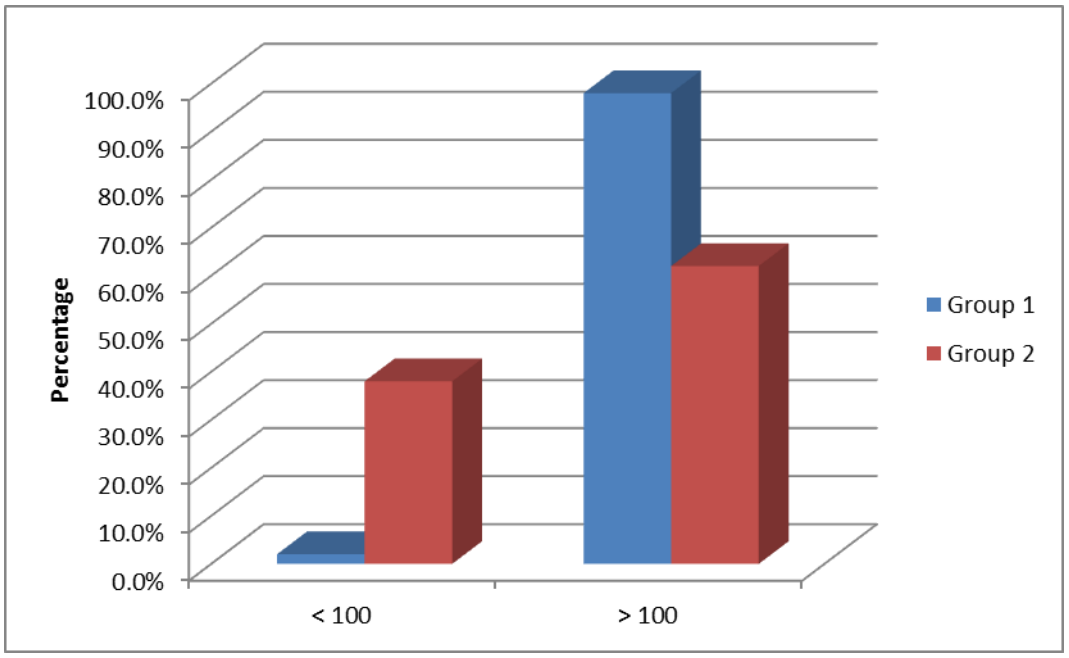

Figure 17: Distribution of patients with serum ferritin levels above and below 100 ng/mL in Group 1 and Group 2

DISCUSSION

This study was done in Department of Nephrology on adults attending OPD or being admitted in Dayanand medical college, Ludhiana.This prospective comparison study intended to assess the safety and effectiveness of iron sucrose vs iron isomaltoside in individuals with anemia and chronic kidney disease (CKD) stage 3-5 ND. One hundred patients were assigned into two groups of fifty each for this study .Group 1 was given a single 1000 mg dose of iron isomaltoside administered over 20 minutes. Group 2 was given iron sucrose intravenously (IV) up to five times over the course of two weeks, for a total dose of 1000 mg. Ten weeks of the study were spent on average, with each patient receiving at least six visits including the 14-day screening phase.

There is currently no IV iron available in India that meets the optimal standards for iron correction and improvement in Hb levels in a single visit, with minimum side effects and a short infusion period. Owing to its structure, isomaltoside 1000/ferric derisomaltose is safe to use at high doses, and numerous studies have shown its effectiveness and safety across a range of demographics and comparators.[51]

Age Distribution

The age distribution in our study was quite similar. In both groups most patients were in the 51–60 and 61–70 age ranges. Although the differences were small, Group 2 had somewhat more patients in the youngest and oldest age groups, whereas Group 1 had slightly more patients in these middle age ranges. 57.80 years is the mean age of Group 1 with a standard deviation of 12.38, while 57.50 years is the mean age of Group 2 with a standard deviation of 11.80. The statistical analysis shows that there is no discernible age difference between the groups.

In their randomized controlled trial, Kalra et al.[60] found that patients with CKD who received oral iron sulphate or iron isomaltoside had a comparable age profile. The iron isomaltoside group had a mean age of 57.63 ± 15.54 years, whereas the iron sulphate group had a mean age of 57.94 ± 16.34 years. In a similar vein, Bhandari et al.'s investigation of iron isomaltoside vs iron sucrose revealed similar age distributions, with mean ages of 60.13± 16.21 and 59.50± 15.39 years, respectively.

It is imperative to ensure comparability and minimize age-related confounding factors in this study by ensuring that there is no substantial age difference between the two groups. The study of Macdougall et al.[61] shows that this similarity in age distribution between treatment groups is a common feature in well-designed comparative research. The mean ages of the iron isomaltoside and iron sucrose groups were 62.7± 14.9 years and 62.9± 15.1 years, respectively.

Gender Distribution

Group 1 had 19 females (38%) and 31 males (62%), while Group 2 had 26 females (52%) and 24 males (48%). Group 2 had a slightly higher proportion of females than Group 1, but there was no statistically significant difference in the gender distribution between the two groups. Group 1 had a higher proportion of males.

This distribution agreed with findings from other related studies. In contrast, Bhandari et al.[28] study of iron isomaltoside against iron sucrose in dialysis patients found a more evenly distributed gender population. In the iron isomaltoside group, they saw 32.5% females and 67.1% men. In the iron sucrose group, there were 63.3% men and 36.8% women, which is more in line with the overall gender balance found in this study. Similar to this, Kalra et al.[60] discovered a fairly

uniform distribution in their study, with 54.2% of male participants and 45.8% of female participants in the iron sucrose group and 39.5% of men and 60.5% of women in the iron isomaltoside group.

As noted by Carrero et al.[62] in their study of sex and gender variations in CKD patients, gender can affect a number of elements of managing anemia and chronic kidney disease.

Clinical Parameters (BMI, Creatinine, eGFR)

Three clinical parameters—BMI, creatinine, and eGFR—were compared between two groups in the current investigation. Compared to Group 2, Group 1 had a marginally higher mean eGFR and BMI but a lower mean creatinine. None of these variations, meanwhile, demonstrates statistical significance.

CKD Stage Distribution

Regarding the differences in stages of CKD between the two groups. The distribution of both groups was comparable in CKD stages 3, 4, and 5. Group 1 had 14% individuals in Stage 3, 36% in Stage 4, and 50% in Stage 5. The distribution in Group 2 was marginally different, with 10% in Stage 3, 36% in Stage 4, and 54% in Stage 5.

Prevalence of Diabetes Mellitus

According to the current investigation, difference between the groups for diabetes mellitus (DM) was not statistically significant, which was identified in 50% of patients in the iron isomaltoside group (Group 1) and 46% of patients in the iron sucrose group (Group 2). Patients with chronic kidney disease (CKD) have a significant prevalence of DM, which is similar to data from multiple previous research. In CKD patients not receiving dialysis, Bhandari S et al. [28] study comparing iron isomaltoside and iron sucrose revealed a greater prevalence of

diabetes mellitus in the iron isomaltoside group (67.5%) and the iron sucrose group (69.3%). The different patient selection criteria or the different phases of CKD that were taken in this study may be the cause of the higher rates.

Diabetes care should be a part of the entire treatment for patients with CKD, as evidenced by the prevalence of DM in these patients, as reported in our study and others. Diabetes is a known risk factor for the advancement of CKD and might make managing anemia more difficult.[63] In order to ensure comparable baseline features and reduce potential confounding factors when comparing the effectiveness of iron isomaltoside versus iron sucrose, it is imperative that the distribution of DM between our study groups be identical.

Use of Erythropoiesis-Stimulating Agents (ESAs)

In this study, erythropoiesis-stimulating drugs (ESAs) were used similarly in the two groups: 74% of patients in Group 2 (iron sucrose) and 70% of patients in Group 1 (iron isomaltoside) received ESAs. The lack of a statistically significant difference indicated that the groups' baseline needs for ESA therapy were similar. The results of our current study were consistent with those of Bhandari et al.'s comparison of iron isomaltoside and iron sucrose in hemodialysis patients, where they reported similar ESA consumption.

Effective iron therapy may eventually lessen the requirement for ESAs, according to several research. At the 52nd Congress of the ERA-EDTA, Leistikow et al.[64] reported an observational study in which they discovered a significant decline in the patients' percentage treated with erythropoiesis-stimulating agents after iron isomaltoside treatment. Biggar et al.[56] found that in certain CKD patients, iron isomaltoside therapy permitted a reduction in ESA dosage.

Hypersensitivity Reactions

This study's comparison of iron sucrose and iron isomaltoside's hypersensitivity reactions shows that there were no statistically significant variations in the incidence of adverse events between the two groups. This result was similar with the generally good safety profiles of both iron formulations as reported by The FERWON-NEPHRO trial, which also showed that there was no discernible difference between the iron sucrose and iron isomaltoside 1000/ferric derisomaltose groups and that serious or severe hypersensitivity reactions happened infrequently.[51]

These occurrences were less than those reported in a prior analysis of IV irons, which found that, in contrast to isomaltoside 1000/ferric derisomaltose, which was defined by a standardized set of MedDRA terms, IS and ferric carboxymaltose were linked to a higher incidence of serious or severe hypersensitivity reactions.[65] The fact that the hypersensitivity reactions documented in the review were not decided upon and verified by an impartial Clinical Endpoint Adjudication Committee, as in the current experiment, may be one reason for this discrepancy. The lack of pruritus in the iron isomaltoside group (Group 1) and its low occurrence (2%) in the iron sucrose group (Group 2) aligns with the results of Bhandari et al[51] who reported low rates of hypersensitivity reactions for both treatments.

Comparable to the findings of Kalra et al.[60], who reported rare instances of infusion-related responses with both iron isomaltoside and iron sucrose, our study also showed low hypersensitivity reactions in both the groups.

These outcomes corroborate those of a more extensive investigation by Auerbach et al.[44], which showed that iron sucrose and iron isomaltoside had comparable safety profiles and low incidence of hypersensitivity events in both groups. Though not statistically

significant, the somewhat decreased incidence of adverse events in the iron isomaltoside group aligns with the findings of Biggar et al[56], who showed a positive safety profile for iron isomaltoside in patients with CKD.

A thorough assessment by Avni et al.[66] indicated that severe hypersensitivity events are uncommon with contemporary intravenous iron formulations, which is consistent with the overall low prevalence of hypersensitivity reactions in both groups in the current investigation. Although not statistically significant, the slightly greater frequency of fever in the iron sucrose group could be attributed to the need for numerous infusions during iron sucrose delivery, as indicated by Macdougall et al[57] in their evaluation of several intravenous iron regimens.

Hemoglobin Levels

The results of this prospective comparative study between iron isomaltoside and iron sucrose in anemic CKD patients complement and enhance other studies in this area. Over time, hemoglobin levels increased in both groups; however, the iron isomaltoside group (Group 1) continuously exhibited higher increases. Hemoglobin levels in Group 1 increased by a mean of 1.28 g/dL by the eighth week, while those in the iron sucrose group (Group 2) increased by 0.99 g/dL, a statistically significant difference of 0.29 g/dL.

This discovery aligns with the outcomes documented in an open-label randomized clinical trial involving NDD-CKD patients by Kalra et al[60]. Their findings demonstrated that Iron isomaltoside 1000 was better than oral iron in terms of hemoglobin increase from Week 3 to Week 8, and non-inferior at Week 4 . When iron isomaltoside dosages were greater than 1000 mg, the hemoglobin reaction was more noticeable.
In their study, Bhandari et al. [51] discovered that the majority (>82%) of participants given with either iron isomaltoside 1000 or iron sucrose

maintained their Hb between 9.5 and 12.5 g/dL at Week 6. This was found in both the FAS and PP populations.Iron isomaltoside 1000 did not do worse than iron sucrose in the non-inferiority test. During Week 6, the majority of subjects treated with either iron isomaltoside 1000 or iron sucrose maintained their Hb between 9.5 and 12.5 g/dL, according to the primary analysis in both the whole analysis set and the per protocol populations (>82%). Iron isomaltoside 1000 did not do worse than iron sucrose in the non-inferiority test.

Additionally, by the eighth week, a greater percentage of patients in the iron isomaltoside group had increased their hemoglobin level to a level that was clinically significant (≥1 g/dL). This was similar to the results of Wikström et al. [41] who found that iron isomaltoside significantly raised hemoglobin levels in CKD patients on dialysis as well as those who were not . Patients treated with TDI experienced a considerably higher rise in hemoglobin than patients receiving bolus dose.

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Six studies were included in a meta-analysis by Rozen-Zvi et al.[67] that compared the effects of oral versus intravenous iron on hemoglobin response in patients with CKD not on dialysis. In five of the six trials, the duration ranged from one to three months. The mean rise in hemoglobin following intravenous iron treatment was 0.31 (95% CI 0.09 to 0.53) g/dL, as compared to oral iron. Nevertheless, a 6-month-long study by Stoves J et al[58] that was included of this meta-analysis showed a mean hemoglobin drop of 0.52 g/dL linked to intravenous iron treatment.

Transferrin Saturation (TSAT) and Ferritin Levels

In terms of iron measures, the study found that starting in the second week, the iron isomaltoside group had considerably greater ferritin and transferrin saturation (TSAT) levels. In Group 1, 94% of individuals obtained the goal TSAT range of 20-50% by the eighth week, but only 76% of participants in Group 2 did so. Comparatively, 62% of patients in the iron sucrose group and 98% of patients in the iron isomaltoside group had ferritin levels above 100 ng/mL. These outcomes were similar to those of Bhandari et al.[28], who discovered that iron isomaltoside and iron sucrose improved iron parameters in hemodialysis patients without being less effective than the other. In their investigation, there were no variations in the mean serum-iron and TSAT concentrations between the two treatment groups at baseline and Week 6. As one may expect, serum ferritin initially rose more with the 500 mg single bolus than with divided doses. The highest mean increase was noted in Week 1, reaching approximately 600 ng/mL. Over the time of next six weeks, there was a consistent decline back to baseline. On the other hand, by Week 6, a continuous rise in split dosing was noted.

Our study's results similarly align with those of Kalra et al.[60], who found that the iron isomaltoside group experienced statistically significant higher increases in TSAT and serum ferritin concentrations from baseline to weeks 1, 2, 4, and 8 in comparison to the oral iron group. This study likewise observed a rapid improvement in iron indices using iron isomaltoside, which is consistent with our findings of significant improvements starting in the second week.

The findings of our investigation were corroborated by Avni et al [66] analysis, which showed that more recent iron formulations, like iron isomaltoside, were successful in quickly raising TSAT and ferritin levels in CKD patients.

Similar to our results, Wikstrom et al[41] reported significant increases in ferritin and TSAT levels, with a significant percentage of patients reaching target ranges. Their research also shown the long-lasting impact of iron isomaltoside on iron-related measures. Ferritin levels for both Monofer (iron isomaltoside) and Cosmofer (iron dextran) increased significantly, According to Sivakumar et al. [68] however, the increase for Cosmofer was greater than that for Monofer (242 µg/L vs.174 µg/L). Despite the fact that the particular iron formulations and comparators used in the trials vary, the variation in ferritin response amongst iron preparations were consistent with our findings. With minor differences in the size of the benefit between different preparations, both investigations confirm the effectiveness of novel iron formulations in improving iron parameters in patients with CKD.

An observational study by Leistikow et al. [64] examined the iron isomaltoside therapy regimen, effectiveness, safety, and tolerability in patients with CKD. The ESA requirement in patients was decreased when iron isomaltoside was administered.

Out of the 1512 patients that Auerbach et al[59] included, 26% had gastrointestinal hemorrhage and 50% had gynecologic hemorrhage. Similar rates of serious or severe hypersensitivity events (0.3% for iron isomaltoside vs. 0.4% for iron sucrose) were observed in both groups, indicating that the primary safety endpoint was fulfilled. Hemoglobin (Hb) change from baseline to week 8 was not significantly worsened by iron isomaltoside, which also showed a noticeably faster and higher Hb response in the first two weeks. When it came to iron isomaltoside, responders percentage (Hb increase ≥2 g/dL) was higher at week 2 (32.6% versus 20.8%). Also, there were greater improvements in tiredness scores at week 1 and week 2 with iron isomaltoside and faster increase in TSAT and serum ferritin.

Agarwal et al[42] examined the effects of oral iron versus intravenous (IV) iron sucrose in patients suffering from iron deficiency anemia and chronic kidney disease (CKD). Compared to oral iron, the study was unable to demonstrate that intravenous iron causes a faster loss in kidney function. Over a 24-month period, hemoglobin levels were similarly raised by IV and oral iron, with no statistically significant difference between the two groups. Serum ferritin and transferrin saturation increased with intravenous iron, especially over the first six months.

Advantages of Iron Isomaltoside

The study's findings suggest that iron isomaltoside's unusual structure, which permits a greater single dosage delivery, may be the reason for its improved efficacy. The work of Jahn et al.[40], which showed the pharmacological benefits of iron isomaltoside over alternative intravenous iron formulations, lends weight to this.

In contrast to iron isomaltoside, iron sucrose has a looser iron bond. This is linked to catalytic or labile iron, which may lead to higher oxidative stress and long-term damage, according to theory.[29]

Effect of iron isomaltoside on iron, TSAT and ferritin

Serum iron levels in CKD patients usually rise a few hours after infusion, which improves iron availability for erythropoiesis. A significant increase in transferrin saturation (TSAT) levels is indicative of this. At the same time, concentrations of ferritin, a measure of iron reserves, significantly rise after treatment with iron isomaltoside. For patients with CKD, who frequently have reduced iron intake and use, these advancements in iron status markers are especially advantageous.

Iron isomaltoside has a tendency to have dose-dependent and persistent effects on these measures, with larger dosages typically producing more noticeable and durable changes. Crucially, iron isomaltoside's ability to quickly replenish iron reserves has been linked to better response to erythropoiesis-stimulating agents (ESAs) and general anemia treatment in patients with CKD, which may lower the need for ESA dosages and enhance quality of life.[28,60]

Table 20: Comparison of our study with other studies

Parameter	Our Study - Iron Isomaltoside	Our Study - Iron Sucrose	Kalra et al. (Iron Isomaltoside)	Kalra et al. (Oral Iron)	Bhandari et al. (Iron Isomaltoside)	Bhandari et al. (Iron Sucrose)	Auerbach et al. (Iron Isomaltoside)	Auerbach et al. (Iron Sucrose)
No. of patients	50	50	-	-	-	-	-	-
Age(years)	57.80 ± 12.38	57.50 ± 11.80	57.63 ± 15.54	57.94 ±16.34	60.13 ± 16.21	59.50 ± 15.39	-	-
M/F(Gender)	62%/38%	48%/52%	39.5%/60.5%	54.2%/45.8%	67.1%/32.9%	63.3%/36.7%	-	-
CKD stage	Stage 3: 14% Stage 4: 36% Stage 5: 50%	Stage 3: 10% Stage 4: 36% Stage 5: 54%	NDD-CKD	NDD-CKD	Hemodialysis patients	Hemodialysis patients	Mixed (26% GI, 50% gynecologic)	Mixed (26% GI, 50% gynecologic)
Diabetes mellitus	50%	46%	-	-	67.5%	69.3%	-	-
ESA Use	70%	74%	-	-	-	-	-	-
Iron Dosing	Single 1000mg dose over 20 minutes	200mg IV injections up to 5 times over 2 weeks	-	oral	-	-	Single 1000mg dose	200mg injections up to 5 times
Hb rise (g/dL)	1.28 g/dL (Week 8)	0.99 g/dL (Week 8)	Superior increase from Week 3 to Week 8	Less increase compared to iron isomaltoside	Maintained Hb between 9.5-12.5 g/dL (>82% of patients)	Maintained Hb between 9.5-12.5 g/dL (>82% of patients)	Non-inferior to iron sucrose at Week 8	-
TSAT (%)	94% (Week 8)	76% (Week 8)	Significantly larger increases	Smaller increases compared to iron isomaltoside	Increased from baseline to Week 6	Increased from baseline to Week 6	Faster increases	Slower increases compared to iron isomaltoside
Ferritin Levels (ng/mL)	98% >100 ng/mL (Week 8)	62% >100 ng/mL (Week 8)	Significantly larger increases	Smaller increases compared to iron isomaltoside	Increased from baseline to Week 6	Increased from baseline to Week 6	Faster increases	Slower increases compared to iron isomaltoside
Hypersensitivity Reactions	Low incidence	Low incidence	-	-	-	-	0.3% (serious or severe)	0.4% (serious or severe)

SUMMARY AND CONCLUSION

SUMMARY

This prospective comparative study aimed to evaluate the safety and efficacy of iron isomaltoside versus iron sucrose in patients with chronic kidney disease (CKD) stage 3-5 with anemia. The study included 100 patients divided into two groups of 50 each. Group 1 was given a single 1000mg dose of iron isomaltoside infused over 20 minutes, while Group 2 was given iron sucrose in 200mg IV injections up to five times over two weeks, for a total dose of 1000mg. The study duration was10 weeks, including a 14-day screening period, with at least six visits per patient. Following observations were noted:

- Age distribution was similar between groups, with no significant difference (p=0.978). Mean age was 57.80 years in Group 1 and 57.50 years in Group 2.
- Gender distribution showed no significant difference (p=0.159).
- No significant differences were found in BMI, creatinine, or eGFR between groups.
- CKD stage distribution was similar between groups (p=0.815).
- Prevalence of diabetes mellitus and ESA use was comparable between groups.
- Pruritus occurred in 2% of Group 2 and 0% of Group 1 and Fever occurred in 4% of Group 2 and 2% of Group 1.
- Both groups showed increasing Hb levels over time. Group 1 had significantly greater increases in Hb at 2nd, 4th, and 8th weeks compared to Group 2 (p=0.001 for all time points). By the 8th week, 90% of Group 1 achieved ≥1 g/dL increase in Hb, compared to 50% in Group 2 (p=0.001).
- Group 1 showed larger increases in TSAT compared to Group 2. Differences became statistically significant at the 4th week (p=0.007) and 8th week (p=0.001). 94% of Group 1 reached the target TSAT range (20-50%), compared to 76% in Group 2

(p=0.023).

- Group 1 showed significantly higher ferritin levels from the 2nd week onwards (p=0.001 for all subsequent time points). By the 8th week, Group 1's mean ferritin level (212.66 ng/mL) was greater than Group 2's (135.43 ng/mL). 98% of Group 1 achieved ferritin levels >100 ng/mL, compared to 62% in Group 2 (p=0.001).

In summary, while both groups were comparable in baseline characteristics, Group 1 (receiving iron isomaltoside) showed significantly greater improvements in hemoglobin, transferrin saturation, and ferritin levels compared to Group 2 (receiving iron sucrose), with no significant differences in adverse effects.

CONCLUSION

Based on the study results, iron isomaltoside demonstrated superior efficacy compared to iron sucrose in treating anemia among patients with CKD stages 3-5 ND. The single 1000mg dose of iron isomaltoside led to significantly greater improvements in hemoglobin levels, transferrin saturation, and ferritin levels over the 10-week study period, without significant increase in adverse effects. Notably, 90% of patients receiving iron isomaltoside achieved a ≥1 g/dL increase in hemoglobin by the 8th week, and a higher proportion reached target transferrin saturation levels and ferritin >100 ng/mL. These findings indicated that iron isomaltoside is not only more effective in correcting anemia and replenishing iron stores but also offers a more convenient treatment option, potentially improving patient compliance and reducing the frequency of hospital visits for iron administration. The comparable safety profile further supports the use of iron isomaltoside as a preferred treatment for anemia in CKD patients. However, longer-term studies are warranted to confirm the sustained efficacy and safety of this approach in managing anemia in the CKD population.

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KEY TO MASTER CHART

M	-Male
F	-Female
Group 1	-Iron Isomaltoside
Group 2	-Iron sucrose
ESA	-Erythropoiesis Stimulating Agents
DM	-Diabetes Mellitus
Hb	-Hemoglobin
TSAT	-Transferrin Saturation
eGFR	-Estimated Glomerular Filtration Rate

Sr. No.	NAME	GROUP	AGE (Years)	GENDER (M/F)	BMI(kg/m2)	CREATININE (mg/dl)	eGFR(mL/min/1.73m2)	CKD STAGE	DM	ESA	HYPERSENSITIVITY REACTION				Hb(g/dL)				
											RASH	PRURITUS	FEVER	ACTUE MI	BASELINE	2ND WEEK	4TH WEEK	8TH WEEK	BASELINE
1	RS	1	60	M	28	4	16	4	Y	Y	N	N	N	N	8.2	8	9.2	7.8	10
2	RM	1	60	F	30	3	17	4	Y	Y	N	N	N	N	8.4	9	9.6	8.2	8.8
3	AS	1	56	M	29	2.1	27	4	Y	Y	N	N	N	N	6.9	7.2	7.8	8.2	9.7
4	DK	1	62	M	31	4.6	14	5	N	N	N	N	N	N	7	7.4	8	8.4	8.6
5	RK	1	54	M	30	2.3	33	3	N	Y	N	N	N	N	7	7.4	8.2	8.6	9.1
6	A	1	43	M	29	4.2	17	4	Y	N	N	N	N	N	6.8	7	7.8	8.8	8.4
7	GK	1	64	F	28	2.1	26	4	N	N	N	N	N	N	7	7.2	7.9	8.6	9.2
8	AS	1	65	F	31	3.2	15	4	Y	N	N	N	N	N	7.1	7.4	8	8.2	9.1
9	P	1	64	F	29	2.4	22	4	N	Y	N	N	N	N	7	7.2	7.8	8	7.4
10	HS	1	54	M	31	2.1	137	3	Y	Y	N	N	N	N	6.8	7.1	7.8	8.2	8.8
11	JG	1	82	M	28	7.2	7	5	N	Y	N	N	N	N	6.4	7	7.2	8.2	9
12	ZS	1	62	M	27	8.4	7	5	N	N	N	N	N	N	7.1	7.3	7.8	8.4	8.1
13	SK	1	55	F	32	3.4	20	4	Y	Y	N	N	N	N	6.8	7.1	8.4	9	7.8
14	RS	1	67	M	31	2.1	34	3	N	N	N	N	N	N	8.1	8.5	9	9.4	9.9
15	A	1	20	M	30	4.1	20	4	Y	Y	N	N	N	N	5.8	6.1	6.4	7	9
16	AP	1	56	M	32	2.4	31	3	N	N	N	N	N	N	7.3	7.7	8	8.5	9
17	TS	1	56	M	33	4.1	16	4	Y	N	N	N	N	N	8.2	8.8	9	9.5	9
18	SK	1	74	F	31	3.9	12	5	Y	Y	N	N	N	N	7.6	8	8.3	8.4	9.8
19	RL	1	62	M	30	5.4	11	5	N	Y	N	N	Y	N	9.8	10.2	10.8	11	8.2
20	RDS	1	56	M	29	6.1	10	5	N	N	N	N	N	N	9.1	9.8	10	10.4	8
21	FC	1	69	M	28	6.9	8	5	Y	N	N	N	N	N	4.7	5	5.2	5.8	7.9
22	NV	1	60	F	30	5.23	9	5	N	Y	N	N	N	N	7.9	8.1	8.4	8.9	6.9
23	DK	1	66	F	31	4.1	11	5	N	N	N	N	N	N	8	8.4	9.1	9.4	19.1
24	SD	1	52	F	33	1.9	31	3	Y	Y	N	N	N	N	7.6	8	8.2	8.9	13
25	H	1	18	F	30	7.1	6	5	N	N	N	N	N	N	6.5	7	7.3	7.9	5.5
26	KS	1	64	M	31	2.1	35	3	N	Y	N	N	N	N	9	9.5	9.8	10.3	12
27	VA	1	59	M	28	4.8	13	5	N	Y	N	N	N	N	6.7	7.1	7.4	8	11
28	AR	1	61	F	27	7.1	6	5	Y	Y	N	N	N	N	7	7.5	7.9	8.4	6.8
29	KK	1	52	F	30	2.1	28	4	Y	Y	N	N	N	N	6.4	6.8	7.1	8	20
30	RS	1	62	M	31	6.1	10	5	N	N	N	N	N	N	7.1	7.6	7.8	8.4	4.6
31	NK	1	72	F	30	4.8	10	5	Y	Y	N	N	N	N	9.4	9.8	10.1	10.6	4.4
32	PK	1	40	F	30	6.1	8	5	Y	N	N	N	N	N	6.1	6.8	7.1	7.9	6
33	MK	1	46	F	31	7.2	7	5	Y	Y	N	N	N	N	7.4	7.8	8.1	8.8	4.4
34	SR	1	61	F	29	4.1	12	5	N	Y	N	N	N	N	7	7.5	7.9	8.5	7.2
35	DN	1	63	M	30	2.9	24	4	N	Y	N	N	N	N	6.4	6.9	7.3	7.8	12
36	GS	1	62	M	29	3.4	20	4	Y	N	N	N	N	N	8.2	8.6	9.1	9.4	10.3
37	JS	1	71	M	31	5.9	10	5	N	Y	N	N	N	N	7.2	7.5	7.8	8.4	13.7
38	GS	1	76	M	33	6.1	9	5	Y	Y	N	N	N	N	8.1	8.4	8.8	9.3	8.8
39	SS	1	62	M	33	8.1	7	5	Y	Y	N	N	N	N	7	7.7	8.1	8.8	17.6
40	RPM	1	68	M	30	2.1	34	3	N	Y	N	N	N	N	6	6.4	6.9	7.3	14.1
41	HS	1	74	M	31	7.1	8	5	Y	Y	N	N	N	N	8.7	9	9.5	10.1	16
42	BS	1	64	M	29	6.8	8	5	N	Y	N	N	N	N	9	9.6	9.9	10.2	6
43	JS	1	60	M	27	2.6	27	4	Y	Y	N	N	N	N	8.6	9	9.4	9.9	16.62
44	KP	1	55	F	30	3.1	17	4	Y	Y	N	N	N	N	6.6	7	7.4	8	14.1
45	R	1	39	M	28	3.4	24	4	Y	Y	N	N	N	N	6.3	6.6	7	7.2	5.4
46	LS	1	53	M	31	5.1	13	5	N	Y	N	N	N	N	9.9	10.1	10.4	11.1	25.4
47	HR	1	55	M	31	6.8	9	5	Y	Y	N	N	N	N	9	9.4	9.9	10.6	18
48	JS	1	55	M	30	7.1	8	5	N	Y	N	N	N	N	7.4	7.8	8.2	8.6	7
49	JK	1	34	F	29	3.6	16	4	N	Y	N	N	N	N	8.1	8.4	8.8	9.4	15.9
50	GS	1	45	F	31	2.9	25	4	N	Y	N	N	N	N	7.6	7.9	8.1	8.4	7.3
51	DN	2	56	M	29	6.1	10	5	Y	Y	N	N	N	N	5.8	6	6.3	6.9	4

Sr. No.	NAME	TSAT (%)			FERRITIN (ng/ml)			
		2ND WEEK	4TH WEEK	8TH WEEK	BASELINE	2ND WEEK	4TH WEEK	8TH WEEK
1	RS	13	15	18	84	100.8	180	200.1
2	RM	12	20	26	91.4	120.4	198	260
3	AS	12	16	24.1	28.7	108	128.5	160.1
4	DK	11.2	14	26.2	36.1	89.1	104.1	156.1
5	RK	11.1	19	24	98	120.4	170.6	200.8
6	A	10.2	17.1	26	71	104.1	140.4	180
7	GK	10.8	20.4	26	84	102	190.1	280
8	AS	10.2	18	28.1	82.1	130	180.4	240
9	P	10.8	18.1	28.8	90.2	168.4	201	290.2
10	HS	10.9	14.6	24.8	87.1	120.2	181.8	260.6
11	JG	10.2	18.6	28.1	98	130.1	164.8	240.9
12	ZS	10.4	19.8	26.4	78.2	120.1	170.2	250.8
13	SK	9	10	12	78	84	102	150
14	RS	10	12.2	14	34.9	98	120	154
15	A	12	18	26	68	120.1	160.4	210
16	AP	10	18.1	28.2	84	150	176	190
17	TS	12	20	28	98	134.1	160.6	250.4
18	SK	12	20	28	96.2	140.6	170.4	210.6
19	RL	11	18	28	80	110	140.6	200.4
20	RDS	10	20	25	94	150	210	280
21	FC	12	28	30	60	100	150.4	190
22	NV	10.5	14.1	20.8	50	58.1	64.7	89.7
23	DK	29.2	36.1	38.4	58.1	150	180	240.4
24	SD	18	20	25	56	104	170	250
25	H	10.1	14	30.2	3.1	48.1	190	240
26	KS	18	21	40	51.8	104	204	270
27	VA	20	26	52	45.2	95	109	190
28	AR	18.6	32	40	22.9	108	140	190
29	KK	25	28	38	12	60	94	140
30	RS	14	20	28	95.2	108	240	300
31	NK	18	29	45	16.9	40.4	70	250
32	PK	12	20	24	16.4	56.4	126.1	180.2
33	MK	10	18.4	20.1	5.2	55.8	104.6	140.6
34	SR	15	21	28	12.5	34	58	100.1
35	DN	20	28	36	97.1	108	150	210.4
36	GS	22	35	46	49.4	78.1	104	190
37	JS	20	27	38	98.1	184	270	310
38	GS	18.1	24.2	31.1	50.7	180	260	306
39	SS	22	29	34	58	108	168	210
40	RPM	20	31	48	47.1	85	140	180
41	HS	26	18	42	56.1	186	209	260
42	BS	16	23	38	72.5	140	190	230
43	JS	24	39	46	56.1	106.1	210.1	240.1
44	KP	21.1	36	42.4	74	112	180.4	210.4
45	R	10.8	16.8	28.6	96	106	156	180
46	LS	30.4	38	56	70.9	99.7	140.1	220.1
47	HR	26	42	48	92.8	160	190	240
48	JS	17	24	29	76.4	116	146	170.1
49	JK	27.1	35	45	41.4	70.1	104.6	150
50	GS	12.5	21	28	10.8	40.1	70.1	190.1
51	DN	8.9	12.9	20	71	280	300	360

Sr. No.	NAME	GROUP	AGE (Years)	GENDER (M/F)	BMI(kg/m2)	CREATININE (mg/dl)	eGFR(mL/min/1.73m2)	CKD STAGE	DM	ESA	HYPERSENSITIVITY REACTION				Hb(g/dL)				
											RASH	PRURITUS	FEVER	ACTUE MI	BASELINE	2ND WEEK	4TH WEEK	8TH WEEK	BASELINE
52	PJ	2	67	M	30	7.1	7	5	N	N	N	N	N	N	9.2	9.5	9.9	10.1	12.2
53	KK	2	59	F	32	8.4	5	5	Y	Y	N	N	N	N	9.4	9.6	9.9	10.3	19.5
54	SS	2	55	M	28	3.4	20	4	N	Y	N	N	N	N	5.2	5.6	5.8	6.2	9.6
55	KK	2	61	F	30	6.8	6	5	N	Y	N	N	N	N	8.2	8.4	8.8	9.4	6.3
56	JN	2	77	M	34	3.1	20	4	Y	N	N	N	N	N	6.2	6.4	6.7	7	4.5
57	DK	2	63	F	31	2.8	18	4	N	Y	N	N	N	N	6.4	6.7	7	7.5	7
58	BK	2	62	F	30	3.4	15	4	N	Y	N	N	N	N	8.2	8.4	8.7	9.1	11.9
59	PS	2	58	M	29	5.1	12	5	Y	Y	N	N	Y	N	7	7.4	7.9	8.3	6
60	NB	2	53	F	30	4.8	10	4	Y	N	N	N	N	N	5.8	6.1	6.3	6.7	6.4
61	T	2	43	F	28	3.1	18	5	N	Y	N	N	N	N	6.8	7.2	7.4	7.7	8
62	SC	2	63	M	27	4.6	14	4	Y	Y	N	N	N	N	6.6	6.9	7.1	7.7	17.1
63	JS	2	66	M	30	7.1	8	4	N	N	N	N	N	N	7.2	7.4	7.8	8.1	6
64	RC	2	66	M	30	2.2	32	3	Y	Y	N	N	Y	N	6.4	6.8	6.9	7.3	4.7
65	SS	2	69	M	31	2.4	28	4	N	Y	N	N	N	N	6.8	7.1	7.3	7.9	8
66	M	2	61	M	32	4.8	13	5	Y	Y	N	N	N	N	6.4	6.6	6.9	7.3	7.3
67	M	2	61	F	31	7.2	6	5	N	N	N	N	N	N	8.8	9	9.3	9.9	9.6
68	HSR	2	71	M	30	7	8	5	N	Y	N	N	N	N	7.8	8	8.2	8.7	8.5
69	BS	2	60	M	28	4.8	13	5	N	Y	N	N	N	N	9.4	9.8	10.1	10.6	8.5
70	RK	2	34	F	26	2	31	3	Y	N	N	N	N	N	7.6	7.8	8	8.2	10.8
71	MR	2	44	F	29	7.1	6	5	N	N	N	N	N	N	7	7.2	7.6	8.1	10.19
72	AK	2	53	M	27	5.8	8	5	Y	Y	N	N	N	N	8.8	9	9.2	9.4	15
73	M	2	53	F	29	4.8	10	5	N	N	N	N	N	N	8.8	9.1	9.3	9.7	18.72
74	AR	2	58	F	31	1.8	8	3	N	Y	N	N	N	N	6.8	7	7.3	7.9	10
75	VK	2	64	M	28	7.1	9	5	Y	N	N	N	N	N	9.8	10	10.2	10.9	13
76	GS	2	60	M	30	6.1	10	5	Y	Y	N	N	N	N	7.4	8.2	8.4	8.7	10.4
77	RK	2	41	F	31	2	32	3	N	Y	N	N	N	N	4.8	5	5.3	5.5	17.19
78	AS	2	61	F	30	4.7	10	5	N	Y	N	N	N	N	6	6.2	6.5	7.1	14.12
79	S	2	62	F	28	6.2	7	5	Y	Y	N	Y	N	N	8	8.3	8.6	9.1	4.1
80	BLG	2	73	M	39	7.1	6	5	Y	Y	N	N	N	N	9.6	9.8	10.1	10.5	16
81	SKS	2	37	F	28	3.1	19	4	N	Y	N	N	N	N	5.4	5.6	5.9	6.3	8.6
82	IP	2	63	F	30	4.1	12	5	Y	N	N	N	N	N	6.4	6.6	6.9	7.5	9.7
83	SR	2	35	F	30	5.1	11	5	Y	Y	N	N	N	N	7.2	7.6	7.9	8.6	12
84	SS	2	32	F	29	6.2	9	5	N	N	N	N	N	N	7.8	7.9	8.1	8.7	5.4
85	S	2	34	F	30	2.8	22	4	N	Y	N	N	N	N	6.4	6.7	6.9	7.4	12.1
86	KK	2	55	F	29	2.1	27	4	Y	N	N	N	N	N	8.8	9	9.3	9.7	14.4
87	SS	2	69	M	28	3.1	21	4	Y	Y	N	N	N	N	7.8	8.1	8.6	8.9	12
88	IS	2	74	M	30	2.5	26	4	N	Y	N	N	N	N	8.8	8.9	9.2	9.7	21.42
89	KK	2	30	F	31	2.9	22	4	N	Y	N	N	N	N	8.2	8.5	8.8	9.4	10
90	RS	2	72	M	29	3.1	21	4	Y	Y	N	N	N	N	6.4	6.8	7.1	7.3	8
91	GK	2	72	F	29	5.4	8	5	N	Y	N	N	N	N	6	6.2	6.5	6.8	10.9
92	BK	2	62	F	28	3.1	16	4	Y	Y	N	N	N	N	9.4	9.8	10	10.5	18.1
93	SS	2	65	M	26	2.4	31	3	N	Y	N	N	N	N	7.8	7.9	8.2	8.7	12.9
94	GS	2	72	M	30	4.1	11	5	Y	Y	N	N	N	N	7.8	8	8.3	8.6	7
95	PR	2	59	F	29	2.8	19	4	Y	Y	N	N	N	N	8.8	9	9.2	9.6	4
96	SS	2	55	M	31	4.8	10	5	Y	Y	N	N	N	N	9	9.2	9.5	9.8	17
97	JK	2	55	F	28	4.1	12	5	N	Y	N	N	N	N	6.7	6.8	7.1	7.7	10
98	SS	2	57	F	32	5.4	9	5	N	Y	N	N	N	N	7.6	7.8	8.1	8.6	5.2
99	MRP	2	47	M	30	6.1	11	5	N	Y	N	N	N	N	7.8	8.1	8.5	8.9	18.4
100	JS	2	56	M	29	4.1	16	4	N	N	N	N	N	N	9	9.3	9.4	10.1	10.02

Sr. No.	NAME	TSAT (%)			FERRITIN (ng/ml)			
		2ND WEEK	4TH WEEK	8TH WEEK	BASELINE	2ND WEEK	4TH WEEK	8TH WEEK
52	PJ	20.1	24.2	29	96.3	150.1	180	220
53	KK	21.5	28.4	39.1	86.1	170.4	210.4	250
54	SS	14.1	20.1	24.4	11.2	40	88.1	104.1
55	KK	12.8	20.8	26	69.7	78	89	190
56	JN	6.8	10.4	15.2	69.18	80.4	98	120
57	DK	9	19	22	88	104	140	180
58	BK	15.4	20	24	23.1	34	56	109
59	PS	10	20	25	6.5	25	48	128
60	NB	12	20	37	91	140	170	210
61	T	15	20	22	20.16	38	56	190
62	SC	22	28	32	54	78	94	120
63	JS	14.1	28.4	30.1	24	58	78	125
64	RC	8.8	15.4	20.2	38.8	50	69.1	104
65	SS	9	11	14	6.7	18	54	91
66	M	10.1	13.2	16	14.2	20	26	98.6
67	M	10.2	12	15.1	13	20.6	32	52.4
68	HSR	9.4	11.6	14.2	32.6	40	44.6	58.1
69	BS	9	9.7	13.1	26.2	28.1	30.4	111.4
70	RK	10.9	12.8	14.1	94	102	124	152
71	MR	14.1	18.2	20.1	48	52.1	68.4	98.2
72	AK	18.4	20	24	92.9	98.1	104.6	130.1
73	M	20.6	24.1	30.7	54.5	60.2	68.9	80.1
74	AR	12.1	14.6	18	92.2	102.1	110.8	140.1
75	VK	15.2	18.1	23.4	62.7	66.8	74.1	188
76	GS	14.8	17.3	24.8	61	70	74.8	90.7
77	RK	20.2	22.2	27.8	55.2	58.4	62.1	79
78	AS	16.8	19.1	24.1	15.4	17.8	30.8	72.4
79	S	4.8	6.2	8.9	21.8	26.1	30.8	90.9
80	BLG	18.1	24.4	30.6	96.5	102.8	116.4	130.8
81	SKS	9.1	10.6	15.6	28.5	34.6	48.5	71.5
82	IP	14.1	18.2	23.7	95.3	104.1	128.2	150.1
83	SR	18.1	20.2	23.2	86	98.2	109.5	240
84	SS	9.8	12.1	17	98.1	104.2	116.1	128.2
85	S	13.8	16.4	20.2	87.9	90.4	108.4	130.9
86	KK	18.6	24.7	30.1	10.34	20.8	48.6	88.1
87	SS	16.2	24.1	30.4	34	38.2	42.4	354
88	IS	25.5	32.1	40.1	56.5	62.8	74.1	90.4
89	KK	13.1	15.2	18.3	13.1	18.2	29.4	85.6
90	RS	12.1	15.3	22	98	104	114.2	167
91	GK	14.9	17.2	25	27	48.1	56.2	98.8
92	BK	20.2	24.6	32	90.8	102.2	114.2	124.8
93	SS	15.4	17.2	28	59.2	68.4	89.1	109.2
94	GS	9.2	14.8	26.1	29.7	32.8	46.4	85.6
95	PR	8.1	12.9	21	3	14.7	19.6	58
96	SS	20.1	24.2	28	10.4	16.4	24.8	98.4
97	JK	12.1	17	22	10.8	20.1	30.8	67.4
98	SS	12.4	15.28	21	98.4	104.6	128.1	150.4
99	MRP	21.3	25.4	28.4	78.1	98.2	104.8	120.4
100	JS	15.1	19.4	28	41.4	50.4	71.4	278.9

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The Principal
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Subject:: Approval of Plan of Thesis.

This is to inform you that the Faculty of Medical Sciences in its meeting held on 25.09.2023 has approved the plan of thesis of **Deepali Kaushal**, a student of your college for **DM Nephrology** along with the names of Supervisor/Co-Supervisor as under:-

Topic Plan of Thesis
Comparative study on safety and efficacy of iron isomaltoside versus iron sucrose in patients of anemia in chronic kidney disease stage 3-5 nd .

Supervisor	**Co-Supervisor:-**	**Co-Supervisor:-**
Dr. Preet Mohinder Singh	Dr. Rajesh Mahajan	Dr. Suman Sethi
Assoc. Prof.,	Professor	Assoc. Professor
Dept. of Nephrology	Dept. of Medicine	Dept. of Nephrology

The student may submit the thesis in triplicate alongwith the plan in triplicate also, to the Controller of Examinations, BFUHS, Faridkot, at least six months before the commencement of theory examination, if he/she is otherwise eligible to take the examination. He /She may be directed to attach a photocopy of this letter with the forwarding letter while submitting thesis in the University along with the letter of approval of University for change of supervisor/Co-Supervisor, change of topic, if any.

Controller of Examinations

Note :

1. *If any discrepancy found regarding topic of thesis or Supervisor/Co-Supervisor, inform undersigned within one month after issue of this letter.*

COMPARATIVE STUDY ON SAFETY AND EFFICACY OF IRON ISOMALTOSIDE VERSUS IRON SUCROSE IN PATIENTS OF ANEMIA IN CHRONIC KIDNEY DISEASE STAGE 3-5 ND

THESIS PROPOSAL

FOR APPROVAL OF SUBJECT OF THESIS TO BE SUBMITTED

IN PARTIAL FULFILMENT OF THE REQUIREMENTS

FOR THE DEGREE OF

DOCTORATE OF MEDICINE

IN

NEPHROLOGY

OF THE

BABA FARID UNIVERSITY OF HEALTH SCINECES

FARIDKOT

SEPTEMBER, 2022

DR. DEEPALI KAUSHAL

DEPARTMENT OF NEPHROLOGY
DAYANAND MEDICAL COLLEGE AND HOSPITAL
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ABSTRACT OF PLAN OF THESIS

Title	COMPARATIVE STUDY ON SAFETY AND EFFICACY OF IRON ISOMALTOSIDE VERSUS IRON SUCROSE IN PATIENTS OF ANEMIA IN CHRONIC KIDNEY DISEASE STAGE 3-5 ND
For the degree of	D. M. Nephrology
Name of the candidate	Dr. Deepali Kaushal
Supervisor	Dr. Preet Mohinder Singh, Associate Professor, Department of Nephrology, DMCH, Ludhiana
Co-supervisor(s)	Dr. Rajesh Mahajan, Professor, Department of Medicine, DMCH, Ludhiana Dr. Suman Sethi, Associate Professor, Department of Nephrology, DMCH, Ludhiana
Institution	Dayanand Medical College & Hospital, Ludhiana
University	Baba Farid University of Health Sciences, Faridkot

Introduction: Patients with CKD who are treated with erythropoiesis stimulating agents are likely to develop iron deficiency due to increased demands for iron. The optimal intravenous iron would allow safe correction of iron deficiency at a single infusion over a short time.

Aim of Study: To evaluate the safety and efficacy of iron isomaltoside in patients with non dialysis dependent chronic kidney disease and iron deficiency anemia.

Materials & Methods: Patients will be randomized into two groups of 50 each , Patients randomized to group 1(iron iso maltoside) will be administered at baseline at a single dose of 1000 mg Patients randomized to group 2 will be administered 200 mg iv injections (5 times) starting at baseline. Each individual will participate in this study for 10 weeks.

Clinical Significance: Compared with multiple doses of iron sucrose ,a single dose of iron isomaltoside can induce a non inferior hematological response and comparably low rates of hypersensitivity reactions.

Keywords: iron isomaltoside 1000,iron treatment,iron deficiency anemia.

(Signature) Candidate | (Signature) Co-supervisor | (Signature) Co-supervisor | (Signature) Supervisor | (Signature) Principal

CERTIFICATE OF FACILITIES AVAILABLE

This is to certify that the facilities for work on the subject of thesis titled **"COMPARATIVE STUDY ON SAFETY AND EFFICACY OF IRON ISOMALTOSIDE VERSUS IRON SUCROSE IN PATIENTS OF ANEMIA IN CHRONIC KIDNEY DISEASE STAGE 3-5 ND"** exist in the Department of Nephrology, DMC&H, Ludhiana and will be provided to the candidate. We will see that the data being included in the thesis is genuine and is collected by the candidate herself under our supervision and guidance.

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APPROVAL PROFORMA
BY
RESEARCH & ETHICAL COMMITTEE
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Department	Nephrology
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Likely date of appearing in PG examination	May/ June, 2024
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Approved: Yes / No

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PROFORMA FOR REGISTRATION OF SUBJECT FOR DISSERTATION

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3	COURSE OF STUDY AND SUBJECT	D.M. Nephrology
4	DATE OF ADMISSION OF COURSE	29.04.2022
5	TITLE OF THE TOPIC	COMPARATIVE STUDY ON SAFETY AND EFFICACY OF IRON ISOMALTOSIDE VERSUS IRON SUCROSE IN PATIENTS OF ANEMIA IN CHRONIC KIDNEY DISEASE STAGE 3-5 ND

6. BRIEF RESUME OF THE INTENDED WORK

6.1 NEED FOR THE STUDY

Anemia is a common complication among patients with chronic kidney disease (CKD), and its prevalence rises as estimated glomerular filtration rate (eGFR) decreases.[1-3] The disorder starts to develop whenthe glomerular filtration rate drops to below 60 ml/min/1..73 m2. Theanemia is rare when the GFR is above 80 ml/min/1..73 m2. As theGFR worsens, the anemia gets more severe. Anemia is generallydefined as hemoglobin of less than 13.0 g/dL in men and less than12.0 g/dL in premenopausal women.[4] Anemia of chronic kidneydisease (CKD) is a form of normocytic normochromic, hypoproliferativeanemia.[5-6] Anemia in CKD is associated with decreased quality of life and increased risk of cardiovascular disease and mortality and cognitive impairment.[7-9]

Anemia in chronic renal disease is a multifactorial condition, the widelyaccepted etiology being decreased renal production of erythropoietin,the hormone that is responsible for the stimulation of red blood cellsproduction. Decreased erythropoietin has recently linked withdownregulation of hypoxia-inducible factor (HIF), a transcription factorthat regulates gene expression of erythropoietin.[10-11] Other mechanisms of CKD-related anemia have also been implicated,[8]including decreased red cell life span,[12] abnormal iron metabolism,[13]chronic inflammation,[14] metabolic abnormalities and effects of medications such as renin angiotensin system (RAS) inhibitors.[15]

Clinical presentation of anemia of renal disease is not different from that of anemia due to other causes. Common symptoms includes: dyspnea, fatigue, generalized weakness, headaches, decreased concentration, dizziness and reduced exercise tolerance. Commonly observable signs include: skin and conjunctival pallor, respiratory distress, tachycardia, chest pain (mostly with severe anemia) and heart failure (usually with chronic severe anemia).[16]

Criteria used to define iron deficiency are different among CKD compared to normal renal function. Among CKD patients, absolute iron deficiency is defined when the transferrin saturation (TSAT) is ≤20%[2] and the serum ferritin concentration is ≤100 ng/mL among predialysis and peritoneal dialysis patients or ≤200 ng/mL among hemodialysis patients. Functional iron deficiency, also known as iron-restricted erythropoiesis, is characterized by TSAT ≤20% and elevated ferritin levels.[17-18]

Treatment of anemia in CKD has come a long way. Before theadvanced treatment options that are available today, the maintreatment option used to be blood transfusions, which came withnumerous complications including infections, hemosiderosis, fluidoverload, transfusion reactions, etc.[19-20] Recombinant humanerythropoietin and darbepoetinalfa are the twoerythropoiesis-stimulating agents generally used in the management ofanemia in CKD. They are fairly similar in efficacy and side effect profile,except for the longer half-life of darbepoetinalfa, thus allowing for lessfrequent dosing.[21-22]

There are many patients with renal failure who will not respondto erythropoiein and this is important as it is an important predictor ofadverse cardiac events. Two factors that lead to unresponsivenessinclude iron deficiency and inflammation. High levels of CRP predictresistance to erythropoietin in dialysis patients. To enhanceresponsiveness to erythropoietin, iron supplements arerecommended.[23]

Iron supplementation is recommended for all CKD patients with anemia. There is general agreement according to guidelines that intravenous (i.v.) iron supplementation is the preferred method for CKD patients on dialysis (CKD stage 5D) and either i.v. or oral iron is recommended for patients with CKD ND (CKD stages 3–5).[24]

Iron isomaltoside is one of the newer IV iron formulations available. It was initially launched in Europe in 2010 and consists of

iron and a carbohydrate moiety where the iron is tightly bound in a matrix structure. It is the matrix structure that enables a controlled and slow release of iron to iron-binding proteins, avoiding potential toxicity from release of labile iron.[25]

Iron sucrose is a brown, sterile, aqueous complex of polynuclear iron (III) hydroxide in sucrose containing 20mg of elemental iron per ml. The sterile solution has an osmolality of 1250mosm/l. the product does not contain preservatives.[26]

This study will be conducted to compare the Safety and efficacy of iron isomaltoside versus iron sucrose in patients of anemia in chronic kidney disease stage 3-5 ND.

6.2 REVIEW OF LITERATURE

Jahn MR et al in 2011[25] compared the physiochemical properties of iron isomaltoside 1000 (Monofer) with the currently available intravenous iron preparations and relates them to their biopharmaceutical properties and their approved clinical applications. The investigated products encompass low molecular weight iron dextran (CosmoFer), sodium ferric gluconate (Ferrlecit), iron sucrose (Venofer), iron carboxymaltose (Ferinject/Injectafer), and ferumoxytol (Feraheme) which are compared to iron isomaltoside 1000 (Monofer). It is shown that significant and clinically relevant differences exist between sodium ferric gluconate and iron sucrose as labile iron formulations and iron dextran, iron carboxymaltose, ferumoxytol, and iron isomaltoside 1000 as stable polynuclear formulations. The differences exist in terms of their immunogenic potential, safety, and convenience of use, the latter being expressed by the opportunity for high single-dose administration and short infusion times. Monofer is a new parenteral iron product with a very low immunogenic potential and a very low content of labile and free iron. This enables Monofer, as the only IV iron formulation, to be administered as a rapid high dose infusion in doses exceeding 1000 mg without the application of a test dose. This offers considerable dose flexibility, including the possibility of providing full iron repletion in a single infusion (one-dose iron repletion).

Wikstrom B et al[26]in 2011 investigated patients with NDD-CKD orstage 5D CKD who were either iron naïve or prepared to switch theirusual IV iron therapy. The primary endpoint was establishment of asafety profile of iron isomaltoside in CKD patients, whereas efficacywas the secondary endpoint. In total, 584 treatments were given (523IV bolus 100 mg, 17 IV bolus 100–200 mg, and 44 high-dose infusions)with single doses up to 1,800 mg. Hb, transferrin saturation, and ferritinincreased significantly, and no acute hypersensitivity reaction ordelayed allergic reactions were reported. It was concluded that ironisomaltoside administered to CKD patients as repeated bolus injections or single high-dose infusion was well

tolerated and resulted inimproved markers of iron status and anemia.

Kalra PA and Bhandari S[27] in 2016 in their review Efficacy and safetyof iron isomaltoside (Monofer®) in the management of patients withiron deficiency anemia stated that New intravenous (IV) ironpreparations should ideally be capable of delivering a wide dosingrange to allow iron correction in a single or low number of visits, a rapidinfusion (doses up to 1,000 mg must be administered over more than15 minutes and doses exceeding 1,000 mg must be administered over30 minutes or more), and minimal potential side effects including lowcatalytic/labile iron release with minimal risk of anaphylaxis.Furthermore, they should be convenient for the patient and health-careprofessional, and cost effective for the health-care system. Theintention behind the development of iron isomaltoside (Monofer®) wasto fulfill these requirements. Iron isomaltoside has been shown to beeffective in 6 treating iron deficiency anemia across multiple therapeuticpatient groups and compared to placebo, IV iron sucrose, and oral iron.Iron isomaltoside consists of iron and a carbohydrate moiety where theiron is tightly bound in a matrix structure. It has a low immunogenicpotential, a low potential to release labile iron, and does not appear tobe associated with clinically significant hypophosphatemia. Due to thestructure of iron isomaltoside, it can be administered in high doses witha maximum single dosage of 20 mg/kg body weight. Clinical trials andobservational studies of iron isomaltoside show that it is an effectiveand well-tolerated treatment of anemia across different therapeuticareas with a favorable safety profile.

Derman R et al[28] in 2017 compared the efficacy and safety of iron isomaltoside (also known as ferric derisomaltose) and iron sucrose in patients with IDA who were intolerant of, or unresponsive to, oral iron. The trial was an open-label, comparative, multi-center trial. Five hundred and eleven patients with IDA from different causes were randomized 2:1 to iron isomaltoside or iron sucrose and followed for 5

weeks. The cumulative dose of iron isomaltoside was based on body weight and hemoglobin (Hb), administered as either a 1000 mg infusion over more than 15 minutes or 500 mg injection over 2 minutes. The cumulative dose of iron sucrose was calculated according to Ganzoni and administered as repeated 200 mg infusions over 30 minutes. The mean cumulative dose of iron isomaltoside was 1640.2 mg and of iron sucrose 1127.9 mg. The primary endpoint was the proportion of patients with aHb increase ≥2 g/dL from baseline at any time between weeks 1-5. Both non-inferiority and superiority were confirmed for the primary endpoint, and a shorter time to Hb increase ≥2 g/dL was observed with iron isomaltoside. For all biochemical efficacy parameters, faster and/or greater improvements were found with iron isomaltoside. Both treatments were well tolerated; 0.6% experienced a serious adverse drug reaction. Iron isomaltoside was more effective than iron sucrose in achieving a rapid improvement in Hb. Furthermore, iron isomaltoside has an advantage over iron sucrose in allowing higher cumulative dosing in fewer administrations. Both treatments were well 7 tolerated in a broad population with IDA.

Jesus-Silva JA et al[29]in 2020 conducted a retrospective observational study in 2 centres designed to compare the safety and efficacy of iron sucrose (IS-Venofer®) versus iron isomaltoside (IIM-Diafer®) in haemodialysis patients. The study included patients currently on dialysis and receiving Venofer who were switched to Diafer® and monitored for at least 12 months for each iron preparation. A total of 190 patients were included and had a mean age of 65.8 years. Non-inferiority was confirmed with no change in mean haemoglobin per mg of iron administered over a 12-month period. In total there were 41,295 prescriptions of iron isomaltoside and 14,685 of iron sucrose with no difference in the number of reported adverse events during the study period. There was a statistically significant effect on Hb over time after conversion, including adjustment for multiple comparisons. There were significant improvements in ferritin over time, which remained at 6 months. The weekly iron dose was similar after adjustment. The EPO dose did not differ significantly after month 0 in

patients switched to IIM. They concluded that Iron isomaltoside is non-inferior to iron sucrose in maintaining Hb in patients on regular haemodialysis/ haemodiafiltration with no difference in the number of reported adverse events.

Ambrosy AP et al[30]in 2021 conducted a randomized, open-label, multi-center clinical trial evaluating the safety and efficacy of a single infusion of FDI 1,000 mgversus up to 5 doses of iron sucrose (IS) 200 mg (recommended cumulative dose, 1,000mg) over 8 weeks in patients with NDD-CKD and iron deficiency anemia. Of 1,525 patientsincluded in the safety analysis, 244 (16%) had a history of heart failure (HF). Overall, therate of serious or severe hypersensitivityreactions was low and did not differ between treatment groups. Cardiovascular adverse events (AEs) were reported for 9.4% of patients who had HF and 4.2% who did not. Time to first cardiovascular AE was longer following administration of FDI compared with IS a difference that was similar in patients with or without HF. Patients achieved a faster hematological response (assessed by changes in hemoglobin and ferritin concentrations, and increase in transferrin saturation) with FDI versus IS. In conclusion, in patients with NDD-CKD, a single infusion of FDIwas safe, well tolerated, and was associated with fewer cardiovascular AEs and a faster hematological response, compared to multiple doses of IS. These effects were similar for patients with and without HF.

Bhandari S et al[31]in 2021 evaluated the safety and efficacy of iron isomaltoside 1000/ferric derisomaltose (IIM) in patients with non-dialysis-dependent chronic kidney disease and iron deficiency anaemia. In this randomized, open-label and multi-centre trial conducted in the USA, patients were randomized 2:1 to a single dose of 1000 mg IIM or iron sucrose (IS) administered as 200mg IV injections up to five times within a 2-week period. The co-primary endpoints were serious or severe hypersensitivity reactions and change in haemoglobin (Hb) from baseline to Week 8. Secondary endpoints included incidence of composite cardiovascular adverse

events (AEs). A total of 1538 patients were enrolled (mean estimated glomerular filtration rate 35.5mL/min/1.73m2). The coprimary safety objective was met based on no significant difference in the incidence of serious or severe hypersensitivity reactions in the IIM and IS groups. Incidence of composite cardiovascular AEs was significantly lower in the IIM versus IS group. Compared with IS, IIM led to a more pronounced increase in Hb during the first 4 weeks, and change in Hb to Week 8 showed non-inferiority, confirming that the co-primary efficacy objective was met. Compared with multiple doses of IS, a single dose of IIM induced a non-inferior 8-week haematological response, comparably low rates of hypersensitivity reactions, and a significantly lower incidence of composite cardiovascular AEs.

6.3 AIMS AND OBJECTIVES OF THE STUDY

- To compare the safety profile of iron isomaltoside versus iron sucrose in patients of anemia in chronic kidney disease stage 3-5 ND.
- To compare the efficacy profile of iron isomaltoside versus iron sucrose in patients of anemia in chronic kidney disease stage 3-5 ND.

7. MATERIALS AND METHODS

7.1 SOURCE OF DATA

Source of data will be patients of CKD stage 3-5 ND

STUDY DESIGN: A prospective comparative study

Investigation (Hb, serum ferritin, transferrin saturation)

Adverse drug reactions (Rash, Pruritus, acute myocardial infarction, Drug hypersensitivity,Infusion related reaction)

Base line

at 2 weeks

at 4 weeks

at 8 weeks

SAMPLING: Random.

7.2 METHOD OF COLLECTION OF DATA

Patients included in the study will be randomized into two groups of 50 eachPatients randomized to group 1 (iron isomaltoside) will be administered at baseline as a single dose of 1000mg infused over 20 min.Patients randomized to group 2 (iron sucrose) will be administered 200mg IV injections repeated up to a maximum of five times within the first week starting at baseline. A cumulative dose of 1000mg will be recommended. Patients randomized to group 2 (iron sucrose) will attend two additional treatment visits to achieve the necessary therapeutic cumulative dose of iron sucrose. Each individual patient will participate in the study for 10 weeks(including a 14-day screening period) during which they will attend at least six visits (screening visit, baseline visit, two assessment visits and final visit).

INCLUSION CRITERIA

- Men or women ≥18 years.
- Haemoglobin ≤11 g/dL
  - Transferrin saturation <20%
  - Serum ferritin <100 ng/ml
- Chronic kidney disease ND, as defined by CKD- Epi - eGFR<60 ml /min//1.73 m2 (not on dialysis)

EXCLUSION CRITERIA

- Haemochromatosis or other iron storage disorders.
- Known hypersensitivity reaction to any component of IIM and IS or previous serious hypersensitivity reactions to any intravenous iron compounds.
- During 10-day period prior to screening; has been treated with intravenous iron.
- During 30-day period prior to screening or during the trial period; has or will be treated with a red blood cell transfusion, radiotherapy, and/or chemotherapy.
- Undergoing dialysis for treatment of chronic kidney disease or under consideration for dialysis during the trial period.
- Any other laboratory abnormality, medical condition, or psychiatric disorders which, in the opinion of the Investigator, will put the patient's disease management at risk or may result in the patient being unable to comply with the trial requirements

DURATION OF STUDY/NUMBER OF CASES: Duration of study will be 10 Weeks(Including 14 days screening period) anda total of 100 patients with anemia in chronic kidney disease stage 3-5 (ND) will be taken.

OUTCOME

Safety (Adverse drug reaction) and efficacy (Haematological response) of iron isomaltoside over iron sucrose.

STATISTICAL ANALYSIS

All the relevant data will be described in terms of range, mean, +/- standard deviation (SD), frequencies (number of cases), and relative frequencies (percentages) as appropriate. Comparison of quantitative variables between the study groups will be done using the Student t-test. For comparing categorical data, the Chi-square(X *) test will be performed and an exact test will be used. A probability value (p-value) less than 0.05 will be considered statistically significant. AII statistical calculations will be done using SPSS 21 (Statistical Package for the Social Science) version statistical program for Microsoft Windows

7.3 DOES THE STUDY REQUIRE ANY INVESTIGATIONS OR INTERVENTIONS TO BE CONDUCTED ON PATIENTS OR OTHER HUMANS OR ANIMALS? IF SO, PLEASE DESCRIBE BRIEFLY.

CBC/RFT (Blood Urea Serum creatinine) serum ferritin transferrin saturation.

7.4 HAS ETHICAL CLEARANCE BEEN OBTAINED FROM YOUR INSTITUTION IN CASE OF 7.3?

Yes, Attached Herewith.

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PROFORMA

S. NO.

NAME

AGE

SEX

RURAL/URBAN

MRD NO

WEIGHT/HEIGHT/BMI

HISTORY

HYPERSENSITIVITY REACTIONS

TREATMENT WITH ESA

CKD STAGE

SIGNATURE OF SUPERVISOR

SIGNATURE OF CANDIDATE

GROUP A

	HB	SERUM FERRITIN	TRANSFERRIN SATURATION	ADVERSE DRUG REACTION
BASELINE				
2ND WEEK				
4TH WEEK				
8TH WEEK				

GROUP B

	HB	SERUM FERRITIN	TRANSFERRIN SATURATION	ADVERSE DRUG REACTION
BASELINE				
2ND WEEK				
4TH WEEK				
8TH WEEK				

OTHERS

RFT- BLOOD UREA

SERUM CREATININE

URINE R/E,

URINE PROTEIN CREATININE RATIO

USG ABDOMEN

SIGNATURE OF SUPERVISOR SIGNATURE OF CANDIDATE

INFORMED PATIENT CONSENT

Date: _____

I……..D/o, W/o, S/o……. ……am willing to participate in the study **"COMPARATIVE STUDY ON SAFETY AND EFFICACY OF IRON ISOMALTOSIDE VERSUS IRON SUCROSE IN PATIENTS OF ANEMIA IN CHRONIC KIDNEY DISEASE STAGE 3-5 ND"** The investigation has been explained to me in local vernacular language. I have fully understood that no extra expenditure in any form, merely for the purpose of thesis is being carried out. I am free to opt out the study any time without assigning any reason.

…….	…….
Signature of the Witness	Signature of the patient / Legal representative
Name:	Name:

Signature of Candidate **Signature of Supervisor**

सूचित रोगी की सहमति

दिनांक: _____

मैं …….. डी/ओ, डब्ल्यू/ओ, एस/ओ ……। ……. मैं **"COMPARATIVE STUDY ON SAFETY AND EFFICACY OF IRON ISOMALTOSIDE VERSUS IRON SUCROSE IN PATIENTS OF ANEMIA IN CHRONIC KIDNEY DISEASE STAGE 3-5 ND"** अध्ययन में भाग लेने के लिए तैयार हूं। जांच के बारे में मुझे स्थानीय स्थानीय भाषा में समझाया गया है। मैं पूरी तरह से समझ गया हूं कि किसी भी रूप में कोई अतिरिक्त खर्च नहीं किया जा रहा है, केवल थीसिस के उद्देश्य से किया जा रहा है। मैं बिना कोई कारण बताए किसी भी समय अध्ययन से बाहर निकलने के लिए स्वतंत्र हूं।

…….. …… ……

गवाह के हस्ताक्षर — रोगी के हस्ताक्षर /कानूनी प्रतिनिधि

नाम — नाम:

उम्मीदवार के हस्ताक्षर — पर्यवेक्षक के हस्ताक्षर

ਸੂਚਿਤ ਮਰੀਜ਼ ਦੀ ਸਹਿਮਤੀ

ਤਾਰੀਖ਼: _____

I……..D/o, W/o, S/o…… ਮੈਂ **“COMPARATIVE STUDY ON SAFETY AND EFFICACY OF IRON ISOMALTOSIDE VERSUS IRON SUCROSE IN PATIENTS OF ANEMIA IN CHRONIC KIDNEY DISEASE STAGE 3-5 ND”** ਅਧਿਐਨ ਵਿੱਚ ਹਿੱਸਾ ਲੈਣ ਲਈ ਤਿਆਰ ਹਾਂ। ਜਾਂਚ ਮੈਨੂੰ ਸਥਾਨਕ ਭਾਸ਼ਾ ਵਿੱਚ ਸਮਝਾਈ ਗਈ ਹੈ। ਮੈਂ ਪੂਰੀ ਤਰ੍ਹਾਂ ਸਮਝ ਗਿਆ ਹਾਂ ਕਿ ਕਿਸੇ ਵੀ ਰੂਪ ਵਿੱਚ ਕੋਈ ਵਾਧੂ ਖਰਚਾ ਨਹੀਂ, ਸਿਰਫ਼ ਥੀਸਿਸ ਦੇ ਉਦੇਸ਼ ਲਈ ਕੀਤਾ ਜਾ ਰਿਹਾ ਹੈ। ਮੈਂ ਬਿਨਾਂ ਕਿਸੇ ਕਾਰਨ ਦੱਸੇ ਕਿਸੇ ਵੀ ਸਮੇਂ ਅਧਿਐਨ ਤੋਂ ਹਟਣ ਲਈ ਸੁਤੰਤਰ ਹਾਂ।

…… ……

ਮਰੀਜ਼ ਦੇ ਗਵਾਹ ਦੇ ਦਸਤਖਤ /ਕਾਨੂੰਨੀ ਪ੍ਰਤੀਨਿਧੀ

ਨਾਮ: ਨਾਮ:

ਸੁਪਰਵਾਈਜ਼ਰ ਦੇ ਉਮੀਦਵਾਰ ਦੇ ਦਸਤਖਤ